In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 17-1109V
Filed: March 5, 2025

LEAH MARSH, as mother and natural guardian of E.M., and JEREMY MARSH, as father and natural guardian of E.M.,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Jeffrey S. Pop, Jeffrey S. Pop & Associates, Beverly Hills, CA, for petitioner.
Neil Bhargava, U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

On August 16, 2017, petitioners filed a petition on behalf of their minor child, E.M., under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10, *et seq.* (2012).[2] (ECF No. 1.) Petitioners allege that the Human Papillomavirus ("HPV") vaccine E.M. received on July 20, 2015, caused her to suffer optic neuritis, as well as a particular form of encephalitis known as Rasmussen's encephalitis. (*Id.* at 1.) They further allege that her November 10, 2015 influenza ("flu") vaccination additionally contributed to the development of her Rasmussen's encephalitis. (ECF No. 59, pp. 1, 15.) For the reasons set forth below, I conclude that petitioners are entitled to compensation for E.M.'s injuries.

[1] Because this document contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the document will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

[2] Within this decision, all citation to § 300aa will be the relevant sections of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury.

In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B). In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In that context, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines ex rel. Sevier v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

In this case, petitioners allege that E.M.'s vaccinations caused her optic neuritis and Rasmussen's encephalitis. Because these injuries are not Table Injuries, petitioners must establish causation-in-fact.[3]

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" with the logical sequence

[3] Encephalitis is a Table Injury relative to some vaccinations, but not either of the vaccinations at issue in this case. 42 C.F.R. § 100.3(a) (as effective March 21, 2017 to January 2, 2022).

being supported by "reputable medical or scientific explanation." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). Ultimately, petitioner must satisfy what has come to be known as the *Althen* test, which requires: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury.[4] *Id*.

A petitioner may not receive a Vaccine Program award based solely on his or her assertions, but may support the petition with either medical records or by the opinion of a competent physician. § 300aa-13(a)(1). Medical records are generally viewed as particularly trustworthy evidence, because they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. § 300aa-13(b)(1). A petitioner may also rely upon circumstantial evidence. *Althen*, 418 F.3d at 1280. In that regard, the *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. While scientific certainty is not required, that expert's opinion must be based on "sound and reliable" medical or scientific explanation. *Boatmon v. Sec'y of Health & Human Servs*., 941 F.3d 1351, 1359 (Fed. Cir. 2019).

Cases in the Vaccine Program are assigned to special masters who are responsible for "conducting all proceedings, including taking such evidence as may be appropriate, making the requisite findings of fact and conclusions of law, preparing a decision, and determining the amount of compensation, if any, to be awarded." Vaccine Rule 3. Special masters must ensure each party has had a "full and fair opportunity" to develop the record but are empowered to determine the format for taking evidence based on the circumstances of each case. Vaccine Rule 3(b)(2); Vaccine Rule 8(a); Vaccine Rule (d). Special masters are not bound by common law or statutory rules of evidence but must consider all relevant and reliable evidence in keeping with fundamental fairness to both parties. Vaccine Rule 8(b)(1). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's

[4] Additionally, petitioners allege that E.M.'s later flu vaccine significantly aggravated her pre-existing condition. However, for the reasons discussed below, it is not necessary to reach that question. Where a petitioner in an off-Table case is seeking to prove that a vaccination aggravated a preexisting injury, the petitioner must establish the three *Althen* prongs along with three additional factors described in the prior *Loving* case. *See Loving ex rel. Loving v. Sec'y of Health & Human Servs.*, 86 Fed. Cl. 135, 144 (2009) (combining the first three *Whitecotton* factors for claims regarding aggravation of a Table injury with the three *Althen* factors for off table injury claims to create a six-part test for off-Table aggravation claims); *see also W.C. v. Sec'y of Health & Human Servs*., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (applying the six-part *Loving* test). The additional *Loving* factors require petitioners to demonstrate aggravation by showing: (1) the vaccinee's condition prior to the administration of the vaccine, (2) the vaccinee's current condition, and (3) whether the vaccinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. *Loving*, 86 Fed. Cl. at 144.

report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." § 300aa-13(b)(1)(A). The special master is required to consider the entirety of record, draw plausible inferences, and articulate a rational basis for the decision. *Winkler v. Sec'y of Health & Human Servs.*, 88 F.4th 958, 963 (Fed. Cir. 2023) (citing *Hines*, 940 F.2d at 1528).

II. Procedural History

Petitioners filed their petition on August 16, 2017, alleging that the HPV vaccine E.M. received on July 20, 2015, caused her to develop both optic neuritis and an autoimmune encephalitis consistent with Rasmussen's encephalitis, and filed medical records to support their claim. (ECF Nos. 1, 7, 10, 15; Exs. 1-22.) Respondent filed his Rule 4(c) report, recommending against compensation, in March of 2018. (ECF No. 16.) Petitioners then filed an expert report with supporting medical literature from neuroimmunologist Dr. Lawrence Steinman. (ECF Nos. 21-24; Exs. 23-58.) Respondent filed responsive expert reports with supporting medical literature from Drs. Christine McCusker (immunology) and Jenny Linnoila (neurology). (ECF Nos. 29-31; Exs. A-C.) The case was then reassigned to the undersigned's docket in June of 2019. (ECF No. 32.)

Petitioners filed a supplemental report and supporting medical literature from Dr. Steinman in November of 2019, and respondent filed additional reports by Drs. McCusker and Linnoila in February of 2020. (ECF Nos. 36, 38-40; Exs. 59-62; Exs. E-F.) Thereafter, petitioners filed updated medical records (ECF No. 43; Ex. 63) and advised that no additional expert reports were needed (ECF No. 41). Therefore, a two-day entitlement hearing was set to commence on March 3, 2022. (ECF No. 44.) However, the hearing was cancelled in February 2022 when petitioners requested an opportunity to pursue the additional theory that E.M.'s subsequent flu vaccine also played a role in the development of her Rasmussen's encephalitis. (ECF No. 48.) The two-day entitlement hearing was rescheduled to commence on December 12, 2022. (ECF No. 51.)

In April of 2022, petitioners filed additional medical records, an expert report from radiologist Dr. Jeffrey Silverman, and a supplemental report from Dr. Steinman. (ECF Nos. 52-54; Exs. 64-88.) Petitioners then filed an amended petition on July 6, 2022, alleging that the HPV vaccination E.M. received on July 20, 2015, caused her to suffer injuries including both optic neuritis and Rasmussen's encephalitis and that her November 10, 2015 flu vaccine, either alone or in conjunction with the prior HPV vaccine, caused Rasmussen's encephalitis. (ECF No. 59, p. 15.) Respondent filed supplemental reports by his experts in August of 2022. (ECF Nos. 61-62; Exs. G-H.) On September 26, 2022, the parties confirmed that the case was ripe for the entitlement hearing. (ECF No. 63.)

The entitlement hearing commenced on December 12-13, 2022; however, it failed to conclude within the allotted time. (ECF No. 97; *see* Transcript of Proceedings ("Tr."), at ECF Nos. 102-03.) The hearing continued on March 28, 2023, and April 17, 2023. (ECF Nos. 100, 105, 108; *see* Transcript of Proceedings ("Tr."), at ECF No. 114; Transcript of Proceedings ("Tr."), at ECF No. 118.) Following the hearing, both parties filed motions for leave to file additional evidence. (ECF Nos. 120-23.) Both motions were granted in part and denied in part. (ECF No. 124.) However, the parties subsequently advised in a joint status report that they did not intend to file additional evidence and that they agreed the record was closed. (ECF No. 125.)

Petitioners filed their post-hearing brief on September 15, 2023; respondent filed his responsive post hearing brief on October 16, 2023; and petitioners filed their reply on November 16, 2023. This case is now ripe for a ruling on entitlement.

III. Medical Conditions Discussed Throughout This Ruling

Demyelination: Demyelination is the loss or destruction of the myelin sheath that covers the axons of the nerves. Demyelination is a manifestation of several conditions that are believed to result from autoinflammatory attacks on the myelin. For example, Guillain-Barre syndrome ("GBS") is a syndrome of ascending polyneuropathy with multiple variants that is believed to be autoimmune. In one form known as Acute Inflammatory Demyelinating Polyneuropathy ("AIDP"), it results in demyelination of the peripheral nerves. Several other conditions, such as optic neuritis and ADEM, as discussed below, cause various patterns of demyelination within the central nervous system.[5]

Optic Neuritis: Optic neuritis is inflammation of the optic nerve. This can be intraocular, affecting the optic disk, or retrobulbar, affecting the portion of the optic nerve behind the eyeball. Optic neuritis can occur in several contexts; however, acute optic neuritis is generally associated with vision loss due to demyelination. Optic neuritis may occur as an isolated, monosymptomatic event, or it may occur as part of a broader primary demyelinating condition affecting the central nervous system, such as neuromyelitis optica ("NMO"), multiple sclerosis ("MS"), or ADEM. Optic neuritis is rarer in children than in adults. Pediatric optic neuritis affects 0.2 per 100,000 children.[6]

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[5] *Demyelination*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=13092 (last visited Jan. 7, 2025); *Demyelination*, STEDMAN'S MEDICAL DICTIONARY (28th ed. 2006); *Guillain-Barré Syndrome*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=110689 (last visited Jan. 7, 2025); *Acute inflammatory demyelinating polyradiculoneuropathy*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=99421 (last visited Jan. 7, 2025); *Polyradiculoneuropathy*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=40276 (last visited Jan. 7, 2025); Melinda Y. Chang & Stacy L. Pineles, *Pediatric Optic Neuritis*, 24 SEMINARS PEDIATRIC NEUROLOGY 122 (2017) (Ex. C, Tab 8, pp. 2-3).

[6] *Optic neuritis*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=92519 (last visited Jan. 7, 2025); *Discus nervi optici*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=70033 (last visited Jan. 7, 2025); Roger Baxter et

ADEM: One of the conditions that may include optic neuritis is "ADEM" or acute disseminated encephalomyelitis. ADEM is an acute syndrome that includes an encephalopathy (*i.e.*, degeneration of the brain) and multifocal demyelinating lesions disseminated throughout the brain. ADEM can have a similar presentation to multiple sclerosis, but is distinguished by being a monophasic condition. ADEM can also resemble autoimmune encephalitis clinically.[7]

Encephalitis: Encephalitis is a debilitating form of progressive encephalopathy that results specifically from inflammation. Typically, it presents clinically with progressive disorientation, confusion, and other cognitive changes. A specific etiology is often unknown. Infection accounts for about half of all identifiable causes of encephalitis.[8]

Autoimmune Encephalitis: Historically, diagnostic criteria for encephalitis assumed an infectious origin. However, beginning in the 2000's, "autoimmune encephalitis" has increasingly been recognized as a category of encephalitides that resemble infectious encephalitis while being non-infectious. Autoimmune encephalitis is a form of immune-mediated disorder and may be idiopathic or paraneoplastic. It represents a "spectrum" of conditions with differing pathophysiology. It can be associated with a number of different, novel neural autoantibodies. However, the absence of autoantibodies does not preclude an immune-mediated encephalitis.[9]

Rasmussen's Encephalitis: Rasmussen's encephalitis is a syndrome "at the frontier of autoimmune encephalitis." It is a chronic inflammatory disease characterized by intractable focal onset seizures, deterioration of neurologic function, and a characteristic progressive atrophy of one side of the brain. The pathogenesis of Rasmussen's encephalitis is not definitively established, but the prevailing understanding is that it involves a cytotoxic T-cell autoimmune response. The extent to which Rasmussen's encephalitis is distinct from "autoimmune encephalitis" and the question of whether it involves an autoantibody response in addition to being T-cell mediated are points of

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al., *Case-Centered Analysis of Optic Neuritis After Vaccines*, 63 CLINICAL INFECTIOUS DISEASES 79 (2016) (Ex. A, Tab 1, p. 1); Raed Behbehani, *Clinical Approach to Optic Neuropathies*, 1 CLINICAL OPHTHALMOLOGY 233 (2007) (Ex. C, Tab 1, pp. 1, 4-5); L.A. Rolak et al., *Cerebrospinal Fluid in Acute Optic Neuritis: Experience of the Optic Neuritis Treatment Trial*, 46 NEUROLOGY 368 (1996) (Ex. C, Tab 2, p. 1); Chang & Pineles, *supra*, at Ex. C, Tab 8, p. 1.

[7] *Acute disseminated encephalomyelitis*, Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=73033 (last visited Jan. 7, 2025); *Encephalopathy*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=16202 (last visited Jan. 7, 2025); Chang & Pineles, *supra*, at Ex. C, Tab 8, pp. 2-3; Francesc Graus et al., *A Clinical Approach to Diagnosis of Autoimmune Encephalitis*, 15 LANCET NEUROLOGY 391 (2016) (Ex. 153, p. 4).

[8] *Encephalitis*, *Dorland's Medical Dictionary Online*, https://www.dorlandsonline.com/dorland/definition?id=16168 (last visited Jan. 7, 2025); Graus et al., *supra*, at Ex. 153, p. 3; Michael J. Bradshaw & Jenny J. Linnoila, *An Overview of Autoimmune and Paraneoplastic Encephalitides*, 38 Seminars Neurology 330 (2018) (Ex. C, Tab 5, p. 4).

[9] Graus et al., *supra*, at Ex. 153, p. 3; Bradshaw & Linnoila, *supra*, at Ex. C, Tab 5, pp. 1, 11.

disagreement in this case. Rasmussen's encephalitis presents primarily in children and is extremely rare, affecting 1-2 per 10,000,000 people.[10]

IV. Factual History

a. Medical Records

E.M. was born on May 1, 2003, and had no significant medical issues prior to onset of her optic neuritis and seizure disorder in 2015. (*See* Ex. 3, p. 1.) She received her first HPV vaccination on February 17, 2015. (Ex. 4, pp. 8-10.) She had a basic eye exam on May 9, 2015, with unremarkable findings. (Ex. 5, p. 2.) E.M. received her second HPV vaccination, one of the vaccinations at issue, on July 20, 2015. (Ex. 2; Ex. 4, pp. 6-7.)

Nearly two months after her second HPV vaccination, E.M. was seen by optometrist Dr. Shawn Beagley on September 15, 2015, for complaints of one month of seeing spots with blurred vision. (Ex. 5, p. 3.) Dr. Beagley assessed E.M. with a papilledema[11] and referred her to ophthalmology. (*Id.*) E.M. then saw ophthalmologist Dr. William Barlow on September 17, 2015. (Ex. 6, p. 1.) Dr. Barlow assessed E.M. with optic nerve edema, noting that the etiology was unclear, and referred E.M. to neuro-ophthalmology. (*Id.*)

E.M. visited neurologic ophthalmologist Dr. Kathleen Digre on September 24, 2015. (Ex. 6, p. 5.) Dr. Digre recorded a medical history of dark spots and tunnel vision since July, originally occurring in both eyes but progressing to only her left eye. (*Id.*) E.M. reported that her vision problems initially occurred almost daily and primarily in the morning; however, her symptoms progressed to affecting her during the day. (*Id.*) E.M. also reported some pain with eye movements, but no headaches or light flashes. (*Id.*) The ocular exam noted a "4+ swelling" in the disk of E.M.'s left eye. (*Id.* at 7-8.) Dr. Digre's impression was that E.M. had a swollen optic nerve on the left with an optic neuropathy, noting that "[t]his could be papilledema from raised intracranial pressure or an optic neuritis." (*Id.* at 9.) Dr. Digre recommended E.M. receive a head/brain MRI, lumbar puncture, CBC and chemical labs, and, if necessary, follow up with pediatric neurology. (*Id.*) E.M. received orbital face/neck and brain MRIs on September 25, 2015. (Ex. 7, pp. 158-60; Ex. 8, pp. 740-43.) The results of E.M.'s orbital face/neck MRI showed an "abnormally enlarged" left optic nerve "with mild protrusion of the optic nerve head and increased T2 signal intensity." (Ex. 8, p. 740.) E.M.'s brain MRI

[10] Graus et al., *supra*, at Ex. 153, p. 31; Lawrence Steinman, *Blocking Immune Intrusion into the Brain Suppresses Epilepsy in Rasmussen's Encephalitis Model*, 128 J. CLINICAL INVESTIGATION 1724 (2018) (Ex. 31, p. 1).

[11] Papilledema is edema, or the presence of an abnormally large amount of fluid, in the intracellular spaces of the optic disk. *Papilledema*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=36673 (last visited Jan. 7, 2025); *Edema*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=15589 (last visited Jan. 7, 2025).

revealed "numerous scattered small foci of T2 hyperintensity in the subcortical white matter," with "no abnormal enhancement following contrast administration to suggest an active demyelinating lesion."[12] (*Id.* at 742.)

E.M. returned to Dr. Digre on October 1, 2015. (Ex. 6, p. 14.) Although E.M. reported that her vision had improved ("[g]ood vision both eyes"), E.M.'s physical and ocular exams were consistent with her previous visit. (*Id.* at 14-16.) At this encounter, Dr. Digre diagnosed left-side optic neuritis with atypical disk swelling, further noting that "this could be more likely a demyelinating disorder such as Acute disseminated encephalomyelitis ["ADEM"] vs multiple sclerosis ["MS"] or other." (*Id.* at 17.) Additionally, Dr. Digre preliminarily concluded E.M.'s condition was related to her prior immunizations, diagnosing ("Post vaccination opti"). (*Id.*; *see also id*. at 14 ("this summer had shots done HPV, ? DPT -- could this be related?"); *id.* at 17 ("will try to get her immunization records to review too").) E.M. was referred to pediatric neurologist Michael Lloyd, M.D., at the Primary Children's Hospital. (*Id.* at 17.)

E.M. presented to Dr. Lloyd on October 8, 2015. (Ex. 8, p. 668.) E.M.'s neurologic exam was normal apart from confirming the presence of optic neuritis. (*Id*. at 669.) Noting that E.M.'s prior MRI showed increased T2 signal in addition to optic neuritis, Dr. Lloyd performed a lumbar puncture to further investigate whether a broader demyelinating disorder was present. (*Id*. at 668-69.) E.M. began a three-day course of Solu-Medrol[13] infusions.[14] (*Id*. at 598, 622, 662, 669, 697.) The lumbar puncture

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[12] As discussed further below, petitioner's radiology expert interpreted the September 25, 2015 MRI as additionally showing a left temporal lobe lesion that may or may not have been included in the reference to "numerous scattered small foci." (Tr. 305.) The parties' experts agree that this lesion would have been part of E.M.'s optic neuritis. (Tr. 423, 425-26 (Dr. Linnoila); Ex. 68, p. 2 (Dr. Silverman).)

[13] Solu-medrol is an intramuscularly or intravenously infused synthetic glucocorticoid that is used as an anti-inflammatory and immunosuppressant in a wide variety of disorders. *Solu-medrol*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=46174 (last visited Jan. 8, 2025); *Methylprednisolone sodium succinate*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=89219 (last visited Jan. 8, 2025); *Methylprednisolone*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=31014 (last visited Jan 8, 2025).

[14] Petitioners contend that E.M. also received a 21-day steroid taper in treatment of her optic neuritis following her infusion treatment. (ECF No. 127, p. 63.) However, in support of this assertion they cite a later history from a medical record dated April 22, 2016. (*Id.* (citing Ex. 134, p. 245).) It is difficult to tell from the contemporaneous medical records whether E.M. actually received a steroid taper in October and November of 2015. E.M.'s hospitalization records confirm that she did begin a prednisone taper at a later time, on January 4, 2016 (*E.g.*, Ex. 8, p. 1221 (noting as of January 5, 2016 that a taper was started "yesterday")), but her earlier treatment records with Dr. Lloyd indicate only that petitioner was prescribed a 3-day course of IV infusions, as well as a course of Vitamin D, when she was being treated for her optic neuritis (Ex. 115, p. 245). Dr. Lloyd's November 10, 2015 consultation report in particular indicates that E.M. was "doing well" after IV Solu-Medrol treatment with no reference to a steroid taper. (*Id.*) However, when E.M. presented for a neurology consult on December 12, 2015, her parents specifically reported a "steroid taper over one month through mid-November, 2015." (Ex. 8, p. 477.) Though a somewhat later record, this is still a treatment record in which E.M.'s parents would have had a motivation to provide an accurate history and is not so far removed from the time the steroid taper would have been administered that it can be completely disregarded. And, because the reports of the prior steroid taper pre-date the

showed low vitamin D, elevated white blood cells, slightly elevated IgM, and "a single [oligoclonal] band in the CSF as well as identical bands present in both the CSF and the serum." (Ex. 134, pp. 721-25.) It was noted that "some individuals with a single band subsequently develop oligoclonal bands several months later," and that "[t]he presence of matching bands is consistent with a systemic immune reaction." (*Id.* at 721.)

E.M. had an outpatient follow up with Dr. Lloyd on November 10, 2015. (Ex. 115, pp. 243-46.) She had tolerated treatment well and reported that she felt her vision was back to normal. (*Id*. at 244.) However, she was still reportedly experiencing intermittent headaches affecting her frontal temporal area, including pain affecting her eyes. (*Id*.) On exam, Dr. Lloyd noted the "[f]undi overall appear clear," but did not specifically indicate whether the previously observed optic disk swelling had resolved. (*Id*. at 245.) Dr. Lloyd interpreted the lumbar puncture results as normal and, after noting that her brain lesions were not in a typical pattern for multiple sclerosis, diagnosed left-sided optic neuritis. (*Id*.) The plan was to monitor and follow up in 3 months unless additional problems arose sooner. (*Id*.) E.M. received her seasonal flu vaccination that day – the second vaccination at issue in this case. (Ex. 8, p. 591; Ex. 2, p. 1.)

E.M. next presented for medical attention on December 9, 2015. At that time, she was brought to the emergency department via ambulance after experiencing an apparent seizure. (Ex. 14, pp. 1-5; Ex. 8, pp. 540-43.) There are conflicting reports as to whether E.M. was suffering an illness in the days prior to her seizure. The EMG records indicate that E.M. "was ill for past 2 days, taking ibuprofen for fever." (Ex. 14, p. 1.) However, a history provided at the hospital indicated that "[m]om said she seemed to be fine in recent days with no recent illness. No fever, no cough, no runny nose, no respiratory symptoms . . . Of note, she had not had any recent illness with any fever." (Ex. 8, p. 578.) A further history indicated she "had no fever or chills. No diarrhea. She does endorse sore throat 2 days prior, headaches day before, but today has been feeling well with no complaints." (Ex. 134, p. 540.) When EMS arrived, they initially recorded that E.M. had an elevated temperature of 100.1ºF. (Ex. 14, p. 1.) However, both parties' experts agree that seizures can elevate body temperature. (Tr. 526-27, 533 (Dr. Linnoila); Tr. 802-03 (Dr. Steinman).) E.M. had a normal body temperature of 37ºC (98.6ºF) by the time she was initially examined in the emergency department. (Ex. 134, p. 541.)

The neurology team recommended another lumbar puncture, a herpes simplex virus ("HSV") test, and prescribed the anticonvulsant Keppra. (Ex. 134, pp. 541, 578-80.) Petitioner's repeat lumbar puncture showed improved, but still elevated, white blood cell count of 24, but no organisms were detected. (*Id.* at 579-80.) Pertinent to the discussion below, testing was also negative for HSV 1 and 2. (*Id*. at 582.) E.M. underwent an EEG, which was interpreted by Dr. Francis Filloux on December 10, 2015, as revealing an abnormal wake and sleep results "due to left hemisphere

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January 4, 2016 taper otherwise confirmed in the records, it is not possible that E.M.'s parents were simply mis-remembering the timing of the later January steroid taper. Respondent's neurology expert, Dr. Linnoila, did base her opinion on the understanding that E.M. was treated with a steroid taper in addition to her infusion. (Tr. 423-24.)

abnormalities consisting of nearly continuous left posterior epileptiform discharges as well as clusters of left hemisphere polymorphic slow waves intermixed with posterior spikes as well as brief periods of nearly 3 per second sharp and slow wave or spike and wave like discharges." (*Id.* at 533.) Dr. Filloux felt that the findings were "consistent with some sort of relatively acute left hemisphere process . . . [and] could be consistent with some form of an epileptic condition." (*Id.*) An additional HSV PCR test was ordered; however, the neurology team felt it was safe to send E.M. home based on the CSF results, given that the pleocytosis had improved since October. (*Id*. at 580.) Discharge diagnoses were new onset of generalized seizure, CSF pleocytosis, and history of optic neuritis. (*Id*.)

E.M. underwent a follow up MRI of the brain on December 12, 2015. (Ex. 8, p. 498.) The impression included focal areas of increased T2 signal in the white matter of both cerebral hemispheres as seen in the prior September MRI and one new lesion in the left periatrial region. (*Id*. at 498-99.) The impression further indicated: "Some of the smaller lesions are no longer detected. None of the lesions show[] enhancement or diffusion restriction. Significance of these lesions is uncertain. They are not typical of the demyelinating lesions of MS, but in the presence of optic neuritis, could represent MS." (*Id*. at 499.) However, the report indicated that "the orbital structures are not specifically studied, as they had been in the past." (*Id*.) Shortly after her MRI, E.M. developed a number of concerning symptoms, including right hand numbness and language deficits, which quickly resolved. (*Id.* at 474.) Accordingly, she was seen in the emergency department by neurologist Dr. Carey Wilson. (*Id.* at 477.) Dr. Wilson reviewed E.M.'s medical history, including her more recent labs and imaging, concluding that her suspicion was "autoimmune encephalitis process as [a] unifying diagnosis," given the continued pleocytosis and progression of symptoms without evidence of an infection. (*Id.* at 478.) She planned to send E.M.'s lab results to Mayo clinic for an autoimmune panel and prescribed an additional course of Keppra. (*Id.*)

E.M. reportedly had two additional seizures lasting two minutes each on December 20, 2015, but she recovered easily. (Ex. 8, p. 467.) She had a further follow up for her seizures with her primary care provider, Dr. Garcia, on December 23, 2015. (Ex. 4, p. 2.) Dr. Garcia reviewed E.M.'s medical history, including her lab results and imaging reports, and noted that E.M. began to experience fever and sore throat three days prior. (*Id.*) It was observed that E.M.'s seizures appeared to coincide with her fevers and that febrile illnesses can lower the seizure threshold. (*Id.* at 2, 4.) It was reported that, on December 22, 2015, E.M. experienced four seizures, each lasting approximately two minutes or less. (*Id.* at 2.) Several different seizures were described as including confusion, twitching, and stiffness. (*Id.*) E.M. had experienced another 30-second seizure on the morning of December 23, 2015. (*Id.*) It was also noted that E.M. was constipated and appeared to be more easily confused. (*Id.* at 2-3.) Dr. Garcia diagnosed petitioner with acute pharyngitis, slow transit constipation, and seizure disorder. (*Id.* at 3.) She recommended that E.M. undergo a neurology evaluation and, in the interim, aggressive treatment of her fevers with over-the-counter medicines. (*Id.*) A strep culture was later reported as negative. (*Id*. at 4.)

E.M. was subsequently admitted to the Riverton Hospital emergency department on December 24, 2015, after experiencing four more seizures over the course of 15 hours. (Ex. 16, p. 33.) E.M.'s mother reported that she was having seizures almost daily since her diagnosis of epileptic seizures earlier that month. (*Id.*) E.M. was postical for several minutes but returned to baseline between the seizures. (*Id.*) E.M. experienced one seizure at the hospital before being treated with Ativan and IV Keppra. (*Id.* at 34.) After E.M. had gone several hours without a seizure, she was discharged home and ordered to follow up with Dr. Lloyd in the following week. (*Id.*) However, E.M.'s mother called Dr. Lloyd's office several times on December 25, 2015, to report that E.M. had experienced four seizures over a "few hour period, each lasting one minute apiece." (Ex. 8, p. 465.) The care provider noted that E.M.'s seizures were escalating and that she had prescribed oxcarbazepine as a new course of treatment. (*Id.*)

On December 28, 2015, E.M. was admitted to the Primary Children's Hospital neurology department with a history of epilepsy and possible autoimmune encephalitis, as well as increased seizure frequency over the past nine days. (Ex. 8, p. 1306.) E.M. presented with a fever and was administered Ativan. (*Id.*) E.M. had reportedly suffered approximately eight or nine seizures earlier in the day, as well as two seizures within 15 minutes of each other prior to her admission. (*Id.*) It was reported that E.M.'s seizures typically last 20-30 seconds and are characterized by right facial twitching. (*Id.*) Although E.M. was usually still responsive during her seizures, she was sometimes unresponsive while seizing with her body falling to the right side. (*Id.*) Her seizures were also occasionally accompanied by fever. (*Id.*) It was noted that the prescribed Ativan initially alleviated her seizures entirely. (*Id.*) However, E.M.'s mother reported that, since December 20, 2015, E.M. had begun acting "more child like." (*Id.*) E.M. had also been experiencing constipation for several days. (*Id.*) E.M.'s physical exam was unremarkable, while her neurological exam revealed dysarthric speech with intermittent response and normal motor function but with decreased reflexes in her bilateral biceps, knees, and ankles. (*Id.* at 1307.) E.M. was admitted for a continuous video EEG to observe further seizure characterization and localization, as well as for medication management of her seizures. (*Id.* at 1309.) During her admission, E.M. underwent near daily sessions of speech and language, physical, and occupational therapies. (*See id.* at 1217-2116.) She was treated with various anticonvulsants, including Ativan, Keppra, oxcarbazepine, clonazepam, lacosamide, phenytoin, and IV fosphenytoin, as well as steroids, including IV Solu-Medrol and prednisone, and plasmapheresis. (*See id.* at 1238-41, 1264-70, 1285-89, 1681-709, 1946-50, 2017-20, 2059-61, 2112-14, 2480-87; Ex. 115, pp. 209-13.) Despite her treatments and therapy, E.M. continued to experience seizures and struggled with fevers, ataxia, aphasia, and dysarthria. (*See* Ex. 8, pp. 1249-52, 1262, 1847, 1946-50, 1955, 2010, 2017-20, 2059-60, 2068, 2076-77, 2095-96, 2103, 2466; Ex. 115, pp. 198-200.)

As of December 29, 2015, the pediatric neurology department had yet to reach a unifying diagnosis and scheduled an additional brain MRI. (Ex. 8, p. 1294.) E.M.'s brain MRI from December 29, 2015, showed increasing T2 signal abnormality compared to her previous imaging. (*Id.* at 1290-91.) The radiologist believed that these

results could show either a transient parenchymal signal change related to the seizures if E.M. was seizing during the MRI, but otherwise, the worsening signal "could represent a glial neoplasm." (*Id.* at 1291.) The absence of diffusion restriction was found to be inconsistent with an ischemic or cerebritis condition, and "[t]he lack of volume loss (and in fact mild thickening of the cortex) argues against Rasmussen encephalitis." (*Id.*) However, the radiologist noted that these findings would require correlation with clinical information and short-term imaging follow ups to track E.M.'s course. (*Id.*)

On December 30, 2015, the pediatric neurology team reviewed E.M.'s brain MRI, noting concerns that she was "becoming progressively encephalopathic with unrelenting seizures from an autoimmune process." (Ex. 8, pp. 1285-88.) The team prescribed continued IV Solu-Medrol for further evaluation of seizures and encephalopathy. (*Id.* at 1286.) E.M.'s autoantibody Ma1 and Ma2 testing from this date revealed no abnormal levels of autoantibodies. (*Id.* at 1754-55.) On December 31, 2015, E.M. received a nephrology consultation in consideration of therapeutic plasma exchanges ("TPE") to treat E.M.'s progressive encephalitis. (*Id.* at 1268.) Dr. Meredith Seamon concluded that E.M. would benefit from TPE and scheduled the various procedures necessary to prepare E.M. for the therapy. (*Id.* at 1270.) Due to E.M.'s troubles with her oral motor skills, beginning on December 31, 2015, she received periodic clinical feeding evaluations during her admission. (*Id.* at 1274-75.) It was noted December 31, 2015 that E.M.'s seizure frequency and mental status improved following her early inpatient treatment with IV Solu-Medrol; however, her treaters planned to initiate plasmapheresis if E.M.'s condition plateaued. (*Id.* at 1278-80.) Plasmapheresis was initiated on January 1, 2016, after E.M.'s condition did not sufficiently improve with the IV Solu-Medrol. (*Id.* at 1264-66.) E.M. received plasmapheresis treatment every other day between January 1, 2016, and January 9, 2016, for a total of five treatments. (*Id.* at 1234, 1253-54, 2117, 2050, 2091.)

A January 2, 2016 neurology note indicates that E.M. was having persistent difficulty with both receptive and expressive components of speech, and that she was likely exhibiting "2/2 L temporal lobe involvement," which was expected to improve with the planned treatment regimen. (Ex. 8, pp. 1249-51.) The note further indicated that, if E.M. did not improve as planned, then she would need additional imaging to evaluate the progression of her condition and for alternative etiologies. (*Id.*) A January 3, 2016 neurology note explains that E.M. experienced a seizure the previous day, after which she experienced Todd's paralysis of her right upper and lower extremities. (*Id.* at 1238-41.) The neurologists believed that this was further evidence of her left temporal lobe involvement. (*Id.* at 1240.) E.M.'s treaters observed that, despite escalating treatments, her seizures persisted. (*Id.*) E.M. was taking Keppra, oxcarbazepine, and phenytoin, but her treating physicians believed that clonazepam could be beneficial without worsening her encephalopathy. (*Id.*) Following her last treatment with IV Solu-Medrol on January 3, 2016, E.M. was started on a prednisone taper on January 4, 2016. (*Id.* at 1222, 1240.)

By January 4, 2016, E.M. was noted to be "doing much better" with her seizures and aphasia. (Ex. 8, p. 1231.) The physician was unsure whether E.M.'s improvement

was due to the IV Solu-Medrol, plasmapheresis, or clonazepam, but chose to continue the existing course of treatment. (*Id.*) A January 6, 2016 neurology note indicated that E.M. was again experiencing facial twitching. (*Id.* at 2113.) An EEG was scheduled to determine whether the conditions were due to her seizures. (*Id.*) E.M. underwent an EEG on January 7, 2016, which showed "very abnormal" results, including the presence of a "marked hemispheric asymmetry with abundant left hemispheric epileptiform discharges." (*Id.* at 2099-100.) There were also "numerous predominantly subclinical seizures arising posteriorly on the left." (*Id.* at 2100.) The frequency, duration, and electrographic severity of E.M.'s seizures lessened as the EEG progressed, and the impression was an epileptic encephalopathy with greater involvement of the left hemisphere. (*Id.*) A January 8, 2016 neurology note indicates that E.M. continued to experience subclinical seizures as observed during the January 7, 2016 EEG, despite having completed a five-day course of IV Solu-Medrol and four plasmapheresis sessions, as well as taking multiple anti-epileptic drugs. (*Id.* at 2077.) E.M.'s clinical seizures had become "infrequent," and she continued to suffer "persistent but improving" expressive and receptive aphasia. (*Id.*) Although E.M. denied sensation to light touch, the reason for her sensory symptoms was unclear. (*Id.*) E.M.'s CSF and MRI findings were noted to be consistent with a possible autoimmune encephalopathy/encephalitis. (*Id.*) E.M. was still scheduled for a final plasmapheresis treatment, at which point the neurology team intended to conduct CT scans to evaluate for possible tumors. (*Id.*) E.M. underwent CT scans of her abdomen, chest, and pelvis that same day. (*Id.* at 2064-67.) Her results were normal with the exception of a large stool burden in her abdomen. (*Id.* at 2047, 2064-67.)

E.M. underwent another EEG on January 9, 2016, which showed some improvement; however, she continued to have seizure activity, aphasia, and difficulty with her gait. (Ex. 8, pp. 2047-48.) On January 10, 2016, it was noted E.M.'s progress had effectively plateaued. (*Id.* at 2047.) The neurology team planned to conduct further imaging to evaluate the progress of her inflammation and, if not improved, to proceed with IVIG or rituximab. (*Id.* at 2048.)

E.M. was referred to the infectious disease team on January 11, 2016. (Ex. 8, pp. 2023-27.) The team considered infectious, post-infectious, and autoimmune etiologies, but felt that an autoimmune cause was most likely, given "the length of symptoms and relapsing remitting episodes." (*Id.* at 2026.) After excluding several causes including fungal etiologies and rabies, the team also noted that:

> There is also the potential that her symptoms may be due to a rare ADEM reaction to the HPV vaccine series. Her symptoms of optic neuritis and subsequent development of seizures occurred within weeks after her second HPV vaccine . . . . Though this temporal relationship does not necessitate causality, there are a few case reports of a similar nature . . . . This could potentially explain the MRI findings, negative infectious CSF work up to date, and symptom progression. A VAERS report should be completed.

(*Id.*) Petitioner was also seen by rheumatology on January 11, 2016. (*Id.* at 2030-33.) The rheumatology team agreed that E.M. was suffering from an autoimmune or autoinflammatory central nervous system disease. (*Id.* at 2033.) An infectious process was deemed unlikely due to the lack of progression during the first two months of E.M.'s course; however, it was noted that E.M.'s initial treatment with steroids could have masked inflammation associated with an indolent infection. (*Id.*) Additionally, although a malignancy was suggested, this too seemed unlikely based on her imaging results. (*Id.*) The team noted that E.M.'s lack of response to corticosteroids and plasmapheresis was troublesome, and they raised some suspicion for neurosarcoidosis or neuro-bechet's. (*Id.*) Other considerations were interferonopathy, Aicardi-goutierre's syndrome, adenosine deaminase type 2 deficiency, lymphomatoid granulomatosis, and lupus, all of which were deemed much less probable. (*Id.*)

E.M. also underwent a further brain MRI on January 11, 2016, which revealed "[i]ncreasing extent and conspicuity of multiple areas of cortical thickening and T2 signal abnormality within the left cerebral hemisphere also involving the adjacent white matter" in the left cerebral hemisphere. (Ex. 8, pp. 2037-38.) Due to the rapid progression of E.M.'s brain lesions over a short period of time, neoplastic process was less likely, though not excluded, and inflammatory process of autoimmune or vasculitic etiology remained a primary differential consideration. (*Id.*) Additional considerations based on E.M.'s early optic neuritis and rapid progression included Bechet's disease, sarcoidosis, or ADEM, although the radiologist noted that E.M.'s CT scans made sarcoidosis less likely. (*Id.*) A January 11, 2016 neurology note recounted E.M.'s treatment course and repeated the group's earlier recommendation for IVIG or rituximab therapy. (*Id.* at 2040.) Differential diagnoses at that time included malignancy; infectious etiology due to consistent pleocytosis; autoimmune encephalitis, despite a negative encephalopathy autoimmune panel; and Rasmussen's encephalitis based on the isolated involvement of E.M.'s left hemisphere and poor response to immunosuppression. (*Id.*) The same day, E.M. had a neurosurgery consult and was scheduled for a brain biopsy to occur on January 14, 2016. (*Id.* at 2043-45.)

E.M. presented to Dr. Carol Bruggers for an oncology consultation on January 12, 2016. (Ex. 8, pp. 2000-03.) After reviewing E.M.'s medical history, treatment course, and imaging results, Dr. Bruggers assessed E.M. with epilepsy and worsening encephalitis with persistent pleocytosis on CSF and abnormal MRI. (*Id.*) Dr. Bruggers indicated that there was concern for malignancy, given E.M.'s MRI findings, and recommended a brain biopsy for tissue diagnosis in order to further distinguish the nature of E.M.'s encephalitis. (*Id.*) Further lab results showed no malignant cells in the CSF. (Ex. 134, p. 2004-05.) A January 12, 2016 flow cytometry report was negative for non-Hodgkin lymphoma. (*Id.* at 2021-22.)

During an infectious disease consultation on January 12, 2016, it was noted that E.M. was not improving, and further testing for less common entities, including for HIV, HSV, CMV, and EBV, was recommended. (Ex. 134, pp. 2009-11.) E.M. underwent extensive testing that same day. (*Id.* at 1339-48.) In pertinent part, E.M. tested positive for HSV Type 1/2 Combined Antibodies, IgM and HSV Type 1 Antibodies, IgG on serum

testing; however, she tested negative for HSV Type 2 Antibodies, IgG on serum testing. (*Id.* at 1341, 1343-44.) She also tested negative for HSV on PCR, as well as negative for both HSV Type 1/2 Combined Antibodies, IgG and HSV Type 1/2 Combined Antibodies, IgM on CSF. (*Id.* at 1343-46.) E.M. also tested negative for both HSV Type 1/2 Combined Antibodies, IgG and HSV Type 1/2 Combined Antibodies, IgM on CSF. (Id. at 1344-45.) A progress note from January 12, 2016, lists differential diagnoses including malignancy, infectious etiology, autoimmune encephalitis, demyelinating process in the central nervous system, Rasmussen's encephalitis, and Gardasil-related ADEM. (*Id.* at 2018.) The physician noted that the mayo clinic returned a negative autoimmune panel and that prior testing were negative for a demyelinating process. (*Id.*)

E.M. underwent another brain MRI on January 13, 2016, which revealed no changes from her previous January 11, 2016 MRI. (Ex. 8, pp. 1986-87.) A January 13, 2016 infectious disease report noted that E.M. continued to be afebrile and suffer multiple seizures throughout the day. (*Id.* at 1988.) It was noted that some case studies have associated adverse immune reactions, including ADEM, with the HPV vaccine, and that such a reaction was being considered in E.M.'s case based on the temporal relationship between her optic neuritis and HPV vaccination. (*Id.* at 1990.) The team noted, however, that this was "a diagnosis of exclusion" and that "autoimmune vs infection etiologies seem the most likely working differential at this point." (*Id.*) E.M. was scheduled for an additional MRI and a brain biopsy. (*Id.*)

The same day, Dr. Thorell, E.M.'s infectious disease specialist, submitted a report to the Vaccine Adverse Event Reporting System ("VAERS"). (Ex. 139, pp. 3-4.) The vaccine reportedly at issue was E.M.'s July 20, 2015 HPV vaccine and the date of the adverse event was noted as September 1, 2015. (*Id*.) The reported adverse event was: "Optic neuritis bilaterally developed 6-7 weeks after her 2nd vaccine. She then developed weakness, behavioral change, dysarthria, facial tics, sensory losses, and difficult-to-manage seizures, w/ multifocal encephalitis, CSF pleocytosis." (*Id*.) It was further explained that a "[b]road workup of autoimmune, infectious, oncologic etiologies over the past month unrevealing so far." (*Id*.) Dr. Thorell explained that

> An inflammatory process of autoimmune or vasculitis etiology remains a primary differential consideration. The absence of true diffusion restriction argues against vasculitis however. Absence of meningeal enhancement and diffusion restriction also argue against infectious cerebritis or meningitis (bacterial or fungal). . . . [A]dditional differential considerations could include Bechet's disease, sarcoidosis, or atypical demyelinating (ADEM) process as unifying diagnoses to explain brain and orbital involvement.

(*Id*. at 2-3)

E.M. then underwent a left frontal lobe biopsy on January 14, 2016, which revealed chronic active encephalitis. (Ex. 19.) E.M. was subsequently transferred to the pediatric intensive care unit ("PICU") for post-operative monitoring following her biopsy. (Ex. 8, pp. 1946-47, 1955.) The PICU admission note indicates that E.M. had

"acute worsening" since January 12, 2016, "with slurred speech and increased seizure frequency (5x/day) and on 1/13 had new onset right sided arm and leg weakness after seizure and also new onset vomiting." (*Id.* at 1955.) She was intubated and provided IV nutrition. (*Id.*) E.M. was also started on IV acyclovir[15] due to the positive serum studies for HSV. (*Id.* at 1908, 1959.) On January 15, 2016, serum samples again were positive for HSV IgG and IgM, and E.M.'s prescribed dose of acyclovir was corrected. (Ex. 134, p. 1334; Ex. 8, pp. 1900, 1936.) There was no evidence of new neurological deficits, and the neurology team planned to taper her steroid treatment post-biopsy. (*Id.* at 1935.) A January 16, 2016 infectious disease report recommended additional CSF and blood labs, indicated that the neurology department planned to administer an additional course of IVIG therapy, and confirmed that a VAERS report was filed. (Ex. 8, pp. 1915-16.) E.M. underwent an MRI spectroscopy on January 17, 2016, which revealed "mild NAA diminution and choline peak elevation compatible with neuronal dysfunction or dropout and membrane turnover." (*Id.* at 1893.) The spectroscopy also showed that E.M.'s myoinositol was mildly elevated, and it was suggested that this finding was "probably related to membrane turnover." (*Id.*)

A January 17, 2016, neurology note indicates that E.M. had a fever, elevated inflammatory markers, a rash, and eosinophilia. (Ex. 8, p. 1898-99.) It was thought that her condition could either be serum sickness related to IVIG therapy or from an infection following her biopsy. (*Id.*) Later, however, Dr. Dodson from the neurology team examined E.M. and found her to be doing "somewhat better," but exhibiting mild extremity weakness with rare clonic movements of the right hand and forearm, which were believed to be simple partial seizures. (*Id.* at 1900-01.) Due to her lack of improvement on acyclovir, E.M. was also started on vancomycin.[16] (*Id.* at 1900.) The following day, on January 18, 2016, the neurology team noted that E.M.'s rash was worsening and that she showed elevated liver enzymes and eosinophils, which was likely indicative of a drug reaction with eosinophilia and systemic symptoms ("DRESS") caused by her anti-epileptic drugs. (*Id.* at 1885.) The team decided to discontinue IVIG therapy and oxcarbazepine, but prescribed topical steroids to treat E.M.'s rash. (*Id.*) Vancomycin and acyclovir were also discontinued due to negative culture and no repeat fevers. (*Id.*) The team prescribed a reduced form of ubiquinol, riboflavin, vitamin C, and carnitine on the off chance that she was suffering from a mitochondrial disease. (*Id.* at 1886.) On January 19, 2016, E.M. was noted to be experiencing increased seizures after discontinuing oxcarbazepine and phenytoin. (*Id.* at 1878.) She was continued on Keppra and prednisone and started on a new anti-convulsant (lacosamide); however, clonazepam was discontinued. (*Id.*)

[15] Acyclovir is a "synthetic acyclic purine nucleoside with selective antiviral activity" that is used in the treatment of HSV. *Acyclovir*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=833 (last visited Jan. 15, 2025).

[16] Vancomycin is an antibiotic that is used to treat cocci (and other gram-positive bacteria), severe staphylococcal infection, staphylococcal enterocolitis, and antibiotic-associated pseudomembranous enterocolitis. *Vancomycin*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=52529 (last visited Jan. 15, 2025).

E.M.'s brain biopsy results were received by the neurology team on January 21, 2016, and showed extensive inflammatory response with peri-neuronal inflammatory cells, perivascular cuffing, extensive gray and white matter edema, no viral particles, no neoplastic cells, and no features consistent with Creutzfeldt-Jakob Disease. (Ex. 8, p. 1854.) The findings were "most consistent with a 'T-Cell mediated' extensive immune mediated or infectious encephalitis." (*Id.*) The infectious disease team additionally observed that "since serum HSV titers had evolved from IgM to IgG response it is not possible to exclude the possibility that HSV could have triggered an immune response in part responsible for this disease (even if there is no evidence of HSV in the brain)." (*Id*.) Although it was noted that Rasmussen's encephalitis is a T-cell mediated autoimmune process and that E.M.'s symptom presentation was consistent with that diagnosis, there remained concern that the MRI imaging was not indicative of Rasmussen's encephalitis and the preceding optic neuritis was atypical. (*Id*. at 1816, 1826, 1835; *see also id.* at 1816 (noting that E.M.'s T-cell mediated encephalitis was "similar to" Rasmussen's encephalitis, but her presentation "does not fit the complete picture" of Rasmussen's).) However, it was felt that immune modulating treatment for an autoimmune process was appropriate. (*Id*.) The neurology team determined that they would begin to treat E.M. with an immune modulator due to increasing suspicion of an autoimmune process at work, as well as acyclovir due to concern for latent HSV infection. (*Id.* at 1816, 1826.) Because E.M. was experiencing several seizures per day, the team decided to increase her prescriptions of lacosamide and clonazepam and continue treatment with Keppra and prednisone. (*Id.* at 1816, 1835.) After consultation between the neurology, neuroimmunology, and rheumatology teams, it was decided that E.M. would be treated with IV rituximab, as well as IV pulse steroids, IVIG, and anti-epileptic drugs. (*Id.* at 1761-67, 1774, 1787, 1789, 1794, 1805.)

Extensive additional medical records are in evidence. E.M. continued to undergo both evaluation and management of her condition and her treating physicians continued to struggle with any definitive diagnosis. However, it is not necessary to discuss the later medical records. Even as the treating physicians remained concerned about the atypical presentation, both parties' experts agree that E.M.'s biopsy and subsequent MRIs demonstrating left hemisphere volume loss are sufficient to confirm her condition as Rasmussen's encephalitis. (Ex. C, pp. 9-11; Tr. 179, 293-94, 396-98, 452-58; Ex. 9, pp. 164-65; Ex. 115, p. 9; Ex. 17, p. 15.) Subsequent to Dr. Thorell's January 13, 2016 VAERS submission, the treating physicians do not appear to have meaningfully discussed likely underlying triggers of E.M.'s condition.

b. Testimony

i. E.M.

During the hearing, E.M. testified briefly and in a limited capacity. (Tr. 9-10.) She confirmed her name and age and that she does not have the use of her right arm and leg. (*Id*.) E.M.'s presence during the hearing demonstrated that she has profound deficits as a result of her injury.

ii. Jeremy Marsh

Petitioner and E.M.'s father, Jeremy Marsh, testified during the entitlement hearing. (Tr. 10-24.) He testified that, in the summer of 2015, he took a trip with his family, during which E.M. was not experiencing any health issues. (*Id.* at 12.) After this trip, E.M. took another trip to see family. (*Id.* at 13.) When E.M. returned home in the beginning of July, she received her second HPV vaccination. (*Id.*) He testified that, after this vaccination, she began reporting some issues with her eyes in the middle of August. (*Id.*) Thereafter, he testified that E.M. had a seizure on December 9, 2015, and was subsequently scheduled for an MRI on December 12, 2015. (*Id.* at 16.) While at the hospital following E.M.'s MRI, petitioner testified that he realized something was wrong when E.M. "looked like she was thinking about what she wanted to say and couldn't remember the words." (*Id.* at 16.) He described how E.M. "couldn't say any words. She couldn't get anything out. She started pulling at her eye and shaking her head, and just couldn't move one of her hands." (*Id.* at 17.)

Mr. Marsh testified that, thereafter, E.M.'s condition progressed, and she was hospitalized from December 28, 2015, until the end of January 2016. (Tr. 18.) He explained that E.M.'s neurologist, Dr. Filloux, found E.M.'s course to resemble atypical Rasmussen's encephalitis. (*Id.* at 19, 21-22.) He testified that, during this time, he was frustrated by the lack of answers as to what caused his daughter's encephalitis. (*Id.* at 18-19.)

Mr. Marsh testified that, before the summer of 2015, E.M. was an excellent student who excelled in math, played the piano, and loved to read and ride her horse. (Tr. 14-15.) Now, E.M. cannot use her right hand and arm. (*Id.* at 19.) She cannot walk without the assistance of a cane and someone standing next to her to help with balance. (*Id.*) He explained that she now has limited cognitive abilities; she can answer simple questions but is easily confused if the questions become too complex. (*Id.* at 20.) She also has a limited vocabulary of less than 10 words. (*Id.*) Petitioner described E.M. as happy and playful, noting that she likes to joke with her siblings. (*Id.*)

iii. Leah Marsh

Petitioner and E.M.'s mother, Leah Marsh, filed an affidavit and provided testimony during the entitlement hearing in this case. (Ex. 1; Tr. 25-65.) Mrs. Marsh testified that E.M. was born on May 1, 2003, with "no significant prenatal problems." (Ex. 1, ¶¶ 2, 4 (citing Ex. 3; Ex. 11, pp. 477, 668).) She testified that, before July 20, 2015, E.M. had no preexisting conditions, was an honor student, and enjoyed playing piano and online games, reading, and horseback riding. (Ex. 1, ¶ 5 (citing Ex. 4, p. 8; Ex. 8, pp. 477, 668, 2001; Ex. 12; Ex. 13).) Specifically, before the summer of 2015, E.M. was in good health and only wore glasses for slight nearsightedness. (Tr. 25-28.)

Mrs. Marsh testified that, in June of 2015, E.M. went on a few trips with family before returning home in July of 2015. (Tr. 28.) During this time, E.M. was completely healthy and active. (*Id.* at 28-29.) She explained that E.M. received her first HPV

vaccination on February 17, 2015, and her second HPV vaccination on July 20, 2015. (Ex. 1, ¶ 6 (citing Ex. 2, pp. 1-2; Ex. 4, pp. 6-9); Tr. 29.) She described how, about a month later, E.M. reported "visual disturbances" and was eventually diagnosed with optic neuritis. (Tr. 31-32; Ex. 1, ¶ 7.) She stated that, in early September 2015, she noticed that E.M. had begun to struggle in school, which was unusual. (Ex. 1, ¶ 8; Tr. 43-44.) Mrs. Marsh went on to summarize E.M.'s medical course prior to her November 10, 2015 flu vaccination. (Ex. 1, ¶¶ 9-14; Tr. 31-48.) She explained that, in October 2015, E.M.'s vision had begun to improve. (Tr. 43-44.) Although E.M. began experiencing headaches, petitioner explained that this symptom was not particularly concerning at that time. (*Id.* at 45-46.) She testified that, in November 2015, E.M.'s doctors recommended against the third dose of the HPV vaccine. (*Id.* at 47.) On November 10, 2015, E.M. was administered the flu vaccine. (*Id.* at 47-48.) E.M. continued to struggle with her schoolwork, but she was no longer complaining of vision issues. (*Id.* at 48; Ex. 1, ¶ 14.) Then, on December 9, 2015, petitioner found E.M. having a seizure and called an ambulance. (Tr. 48-49; Ex. 1, ¶ 15.) Mrs. Marsh went on to summarize E.M.'s medical course including her emergency room visits and subsequent Rasmussen's encephalitis diagnosis. (Tr. 49-55; Ex. 1, ¶¶ 16-27.) She explained her understanding of the atypical diagnosis as stemming from how quickly E.M.'s condition progressed and the fact that Rasmussen's encephalitis usually occurs in much younger patients. (Tr. 64.) She testified that, throughout December 2015 and January 2016, E.M.'s condition continued to progress with an increase in seizure frequency. (*Id.* at 51-52.) She stated that, eventually, Dr. Filloux filed a VAERS report because, after ruling out other possible causes, E.M.'s treaters had not found any other cause for her condition. (*Id.* at 54.)

Petitioner averred that, "E.M. continues to experience severe sequelae of encephalitis, including but not limited to progressive left side cerebral atrophy." (Ex. 1, ¶ 29.) E.M.'s condition has left her unable to use her right arm and leg, and she "endures constant facial twitching." (*Id.*) "[E.M.] is severely limited in nearly every activity in her daily life," and "these diminishments are permanent." (*Id.*)

V. Expert Opinions

a. Petitioners' Experts

i. Lawrence Steinman, M.D.

In support of their claim, petitioners presented an expert opinion by neuroimmunologist Lawrence Steinman, M.D. Dr. Steinman submitted three expert reports and provide testimony during the entitlement hearing. He was offered without objection as an expert in neurology, immunology, and neuroimmunology.[17] (Exs. 23,

[17] Dr. Steinman received his medical degree from Harvard University in 1973. (Ex. 24, p. 1; Tr. 67..) He is board-certified in neurology and practices at Stanford University, where he also serves as a Professor of Neurology. (Ex. 24, pp. 1-2; Ex. 23, p. 1; Tr. 66-69.) Dr. Steinman has treated patients, both adults and children, who suffered from various forms of inflammatory neuropathy, including optic neuritis, transverse myelitis, ADEM, neuromyelitis optica, multiple sclerosis, and others. (Ex. 23, p. 1; Tr. 70-71.) Dr. Steinman's research focuses on how the immune system attacks the nervous system, and he has

59, 69; Tr. 77.) Dr. Steinman opined that E.M. suffered from optic neuritis, characterized by inflammation of the optic nerve, as well as "an autoimmune seizure disorder with *epilepsia partialis continua* (EPC) affecting one hemisphere greater than the other, likely Rasmussen's encephalitis." (Ex. 23, p. 15 (citing ***Rasmussen's Encephalitis Information Page***, NAT'L INSTS. OF HEALTH: NAT'L INST. OF NEUROLOGICAL DISORDERS & STROKE (June 6, 2015) (Ex. 30), Steinman, *supra*, at Ex. 31); Tr. 77-80.) Dr. Steinman testified that his assessment of the case can be boiled down to three medically reasonable possibilities: (1) the HPV vaccine caused both E.M.'s optic neuritis and Rasmussen's encephalitis[18]; (2) the HPV vaccine and flu vaccine acted synergistically to cause E.M.'s overall condition; or (3) the HPV vaccine caused E.M.'s optic neuritis and, separately, the flu vaccine caused her Rasmussen's encephalitis. (Tr. 214, 229.) Pertinent to the analysis that follows, Dr. Steinman explained that, in a "two-hit" model of Rasmussen's encephalitis, E.M.'s optic neuritis lesions could have "exploded into what we call Rasmussen's" encephalitis with the flu vaccine acting as a second necessary "hit," stressing that both conditions are autoinflammatory. (*Id.* at 200-04, 214, 233-34, 248, 776-77.) This is his preferred explanation for E.M.'s condition (*Id.* at 220, 229), and he asserted that it withstands respondent's contention that optic neuritis and Rasmussen's encephalitis involve distinct pathologies. (*Id.* at 212-14.)

Dr. Steinman explained that "Rasmussen's encephalitis is a rare, chronic inflammatory neurological disease that usually affects only one hemisphere of the brain." (Ex. 23, p. 15 (quoting ***Rasmussen's Encephalitis Information Page***, *supra*, at Ex. 30); Tr. 83-84.) It typically occurs in children under the age of ten and results in "frequent and severe seizures, loss of motor skills and speech, paralysis on one side of the body (hemiparesis), inflammation of the brain (encephalitis), and mental deterioration." (Ex. 23, p. 15 (quoting ***Rasmussen's Encephalitis Information Page***, *supra*, at Ex. 30).) He noted that the typical disease course is characterized by eight to twelve months of progressive brain damage followed by permanent neurological deficits. (*Id.* (citing ***Rasmussen's Encephalitis Information Page***, *supra*, at Ex. 30).) Dr. Steinman explained that E.M.'s Rasmussen's encephalitis has led to continuous seizures, or *epilepsia partialis continua*. (Tr. 86-87.) He noted that, like ADEM, Rasmussen's encephalitis can have an autoimmune pathophysiology that, specifically, involves cytotoxic T cells. (Tr. 180-81, 778-79 (citing Graus et al., *supra*, at Ex. 153, p. 31), 781-82 (citing A. Orsini et al., ***Rasmussen's Encephalitis: From Immune Pathogenesis Towards Targeted-Therapy***, 81 SEIZURE: EUR. J. EPILEPSY 76 (2020) (Ex. G, Tab 2)).)

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published on various topics involving vaccines and neurological disorders, including molecular mimicry. (Ex. 23, p. 3; Tr. 70.) He holds numerous American and European patents, including several U.S. patents relating to vaccines. (Ex. 23, p. 4.) Dr. Steinman is a listed author on over 550 publications, including one on Rasmussen's encephalitis and several on optic neuritis and molecular mimicry. (Ex. 24, pp. 5-46; Tr. 71-73, 76.)

[18] In support of this theory, Dr. Steinman included a discussion of cross-reactive potential between components of the HPV vaccine and glutamate receptors that have separately been implicated in the pathophysiology of Rasmussen's encephalitis. However, in light of the analysis that follows, it is not ultimately necessary to fully address that aspect of Dr. Steinman's opinion. The fact of this aspect of Dr. Steinman's theory is briefly discussed in note 39, *infra*, but is noted to be beyond what petitioners ultimately need to demonstrate.

Although two distinct conditions, Dr. Steinman opines that E.M.'s optic neuritis and Rasmussen's encephalitis can be causally related. (Ex. 23, p. 15 (citing *Rasmussen's Encephalitis Information Page*, *supra*, at Ex. 30; Steinman, *supra*, at Ex. 31).) He acknowledged that the scientific literature does not specifically report cases of optic neuritis associated with Rasmussen's encephalitis, but referenced case reports of ocular inflammation, namely uveitis, preceding Rasmussen's encephalitis. (*Id.* (citing A. Simon Harvey et al., *Chronic Encephalitis (Rasmussen's Syndrome) and Ipsilateral Uveitis*, 32 ANNALS NEUROLOGY 826 (1992) (Ex. 33); Tokiko Fukuda et al., *Chronic Localized Encephalitis (Rasmussen's Syndrome) Preceded by Ipsilateral Uveitis: A Case Report*, 35 EPILEPSIA 1328 (1994) (Ex. 34)).) While only optic neuritis is a demyelinating condition, both conditions are inflammatory in nature. (Tr. 183, 204-05, 233.) In particular, Dr. Steinman noted that E.M.'s MRI after her optic neuritis diagnosis showed "some evidence of a pathological process going on outside the optic nerve," in her left temporal lobe, which he concluded meant that "the process was more widespread than just the optic nerve." (*Id.* at 157-58.) Even after E.M. had a good clinical recovery from her optic neuritis, E.M. still had ongoing optic neuritis radiologically which, according to Dr. Steinman, indicates ongoing inflammation at the time of her subsequent flu vaccine and development of Rasmussen's encephalitis. (*Id.* at 158-59.) In particular, while E.M.'s December 12, 2015 MRI did not specifically examine her orbits, Dr. Steinman noted that her subsequent December 29, 2015 MRI confirmed continued enhancement of the optic nerve, consistent with ongoing optic neuritis.[19] (*Id.* at 766-67.)

Dr. Steinman opined that the HPV vaccine has components that "are immunologically cross-reactive with components on neurons and myelin." (Ex. 23, p. 17 (citing Gardasil [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] Package Insert (2011) (Ex. 35) [hereinafter Gardasil Package Insert]; Lawrence Steinman, *Autoimmune Disease: Misguided Assaults on the Self Produce Multiple Sclerosis, Juvenile Diabetes and Other Chronic Illnesses. Promising Therapies Are Emerging*, 269 SCI. AM. (SPECIAL ISSUE) 106 (1993) (Ex. 36)).) He explained that the Gardasil vaccine "is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18." (*Id.* (citing Gardasil Package Insert, *supra*, at Ex. 35); Tr. 88-89.) In particular, he noted that the L1 protein is an external protein of the virus that the vaccine makes accessible to the immune system. (Tr. 89.) Moreover, Dr. Steinman explained that Gardasil "elicits a stronger immune response than the natural viral infection," meaning vaccination induces more antibodies than infection. (Ex. 23, p. 19 (citing Nizar Souayah et al., *Guillain-Barré Syndrome After Gardasil Vaccination: Data from Vaccine Adverse Event Reporting System 2006-2009*, 29 VACCINE 886 (2011) (Ex. 39)); Tr. 90-

[19] Dr. Steinman opined further on E.M.'s MRIs from September 2015 to December 2015. (Tr. 157-61.) I have reviewed Dr. Steinman's testimony in its entirety; however, because he ultimately agrees with Dr. Silverman (*Id.* at 161), it is not necessary to separately summarize Dr. Steinman's opinion regarding the MRIs.

91.) Dr. Steinman opined that this is significant because it generally shows a stronger response to vaccination than to a natural infection. (Tr. 91-93.)

Dr. Steinman noted that "[o]ne of the main antigens that drives optic neuritis is an immune response to a myelin protein known as MOG" (Myelin oligodendrocyte glycoprotein). (Ex. 23, p. 20 (citing Estelle Bettelli et al., *Myelin Oligodendrocyte Glycoprotein-Specific T Cell Receptor Transgenic Mice Develop Spontaneous Autoimmune Optic Neuritis*, 197 J. EXPERIMENTAL MED. 1073 (2003) (Ex. 43); Lawrence Steinman, *Optic Neuritis, A New Variant of Experimental Encephalomyelitis, A Durable Model for All Seasons, Now in its Seventieth Year*, 197 J. EXPERIMENTAL MED. 1065 (2003) (Ex. 44); Kimihiko Kaneko et al., *CSF Cytokine Profile in MOG-IgG+ Neurological Disease is Similar to AQP4-IgG+ NMOSD but Distinct from MS: A Cross-Sectional Study and Potential Therapeutic Implications*, 89 J. NEUROLOGY NEUROSURGERY & PSYCHIATRY 927 (2018) (Ex. 45); Yael Hacohen et al., *Myelin Oligodendrocyte Glycoprotein Antibodies are Associated with a Non-MS Course in Children*, 2 NEUROLOGY NEUROIMMUNOLOGY & NEUROINFLAMMATION 1 (2015) (Ex. 46)); Tr. 96, 132.)[20] Dr. Steinman performed BLAST[21] searches for MOG and components of the Gardasil vaccine (specifically, the HPV 16 and HPV 18 viral proteins) and identified sequences of identical amino acids that he opined were sufficient to trigger neuroinflammation as demonstrated experimentally by animal models. (Ex. 23, pp. 24-29 (citing Anand M. Gautam et al., *A Viral Peptide with Limited Homology to a Self Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis*, 161 J. IMMUNOLOGY 60 (1998) (Ex. 51); Anand M. Gautam et al., *Minimum Structural Requirements for Peptide Presentation by Major Histocompatibility Complex Class II Molecules: Implications in Induction of Autoimmunity*, 91 PROC. NAT'L ACAD. SCIS. USA 767 (1994) (Ex. 52); Anand M. Gautam et al., *A Polyalanine Peptide with Only Five Native Myelin Basic Protein Residues Induces Autoimmune Encephalomyelitis*, 176 J. EXPERIMENTAL MED. 605 (1992) (Ex. 53)); Tr. 129-32, 134-35.) Further to these animal models, Dr. Steinman presented a study by Lanz et al., in which this degree of homology was confirmed as a molecular mimic between the Epstein-Barr virus and glialCAM within human subjects in the context of multiple sclerosis. (Tr. 150-54; Tobias V. Lanz et al., *Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 and GlialCAM*, 603 NATURE 321 (2022) (Ex. 71).)[22] Dr. Steinman acknowledged that

[20] The article by Kaneko et al. that was filed into evidence is noted to be an "Epub ahead of print"; however, the article has since been published and is herein cited in accordance with the publication information that is available on PubMed at https://pubmed.ncbi.nlm.nih.gov/29875186/.

[21] Basic Local Alignment Search Tool or "BLAST" is a program that "compares nucleotide or protein sequences to sequence databases and calculates the statistical significance of matches." *Basic Local Alignment Search Tool*, NAT'L LIBR. MED., https://blast.ncbi.nlm.nih.gov/Blast.cgi (last visited Jan. 21, 2025). BLAST searches "can be used to infer functional and evolutionary relationships between sequences as well as help identify members of gene families." *Id.*

[22] The article by Lanz et al. that was filed into evidence is noted to be an "Accelerated Article Preview" and is without publication details beyond the date of online publication. The Lanz article is herein cited in accordance with the publication information that is available on Nature at https://www.nature.com/articles/s41586-022-04432-7.

molecular mimicry is widespread; however, he asserted that he "increase[s] the relevance of the molecular mimics" by using the Immune Epitope Data Base to filter and ensure the mimics match his criteria. (Ex. 59, pp. 3-7.)

Dr. Steinman acknowledged that a study by Baxter et al. found no statistically significant epidemiologic relationship between the HPV vaccine and optic neuritis. (Ex. 59, pp. 1-2 (citing Baxter et al., *supra*, at Ex. A, Tab 1).) However, he explained that the study listed several limitations and noted that "safe by epidemiological standards" does not mean that the vaccination did not cause petitioner's condition in this specific case. (*Id.*) Dr. Steinman cited a different study that identified an increased risk of optic neuritis following the second dose of the HPV vaccine. (Ex. 23, p. 20 (citing Gayathri Sridhar et al., *Evaluation of Optic Neuritis Following Human Papillomavirus Vaccinatio*n, 13 HUM. VACCINES & IMMUNOTHERAPEUTICS 1705 (2017) (Ex. 40; Ex. A, Tab 4)); Tr. 135-36.)

Dr. Steinman also offered molecular mimicry as the theory by which Rasmussen's encephalitis can develop. (Ex. 23, p. 17 (citing Steinman, *supra*, at Ex. 36); Tr. 101-02 (citing Yukitoshi Takahashi, *Infections as Causative Factors of Epilepsy*, 1 FUTURE NEUROLOGY 291 (2006) (Ex. 85)); Ex. 69.) Following a subacute or prodromal phase, T cells cross-react with glutamate receptors in the central nervous system leading to autoantibodies and Rasmussen's encephalitis.[23] (Ex. 23, p. 17; Tr. 101-05 (citing Takahashi, *supra*, at Ex. 85, p. 3, figs.1 & 6); *see also* Anjan Nibber et al., *Antibodies to AMPA Receptors in Rasmussen's Encephalitis*, 20 EUR. J. PAEDIATRIC NEUROLOGY 222 (2016) (Ex. 48); Sophia Varadkar et al., *Rasmussen's Encephalitis: Clinical Features, Pathobiology, and Treatment Advances*, 13 LANCET NEUROLOGY 195 (2014) (Ex. 49); Yukitoshi Takahashi et al., *Autoantibodies and Cell-Mediated Autoimmunity to NMDA-Type GluRε2 in Patients with Rasmussen's Encephalitis and Chronic Progressive Epilepsia Partialis Continua*, 46 EPILEPSIA 152 (2005) (Ex. 50).)

[23] In light of the analysis that follows, it is not necessary to address the specific link that Dr. Steinman seeks to draw between the flu vaccine and the glutamate receptors. Briefly, Dr. Steinman performed a BLAST search and identified a peptide sequence from the influenza A hemagglutinin protein, which was a component in the 2015-2016 flu vaccine, with 7 out of 12 homology with the NMDA-R-glutamate receptor epsilon 2. (Ex. 69, p. 5; Tr. 94 (citing *Influenza Virus Vaccine for the 2015-2016 Season: Cumulative 2015/2016 Season Lot Release Status*, FED. DRUG ADMIN. (last updated Dec. 16, 2015) (Ex. 73)), 144-49.) Dr. Steinman explained that the hemagglutinin protein serves a similar purpose as the L1 protein in the HPV vaccine. (Tr. 89.) Additionally, hemagglutinin has been identified as a potential cross-reactive molecule with glutamate receptors associated with Rasmussen's encephalitis. (*Id.* at 105-06 (citing Yukitoshi Takahashi, *supra*, at Ex. 85, p. 3, fig.4).) Dr. Steinman also explained that T cell cross reactions between components of the flu vaccine and glutamate receptors have been identified by lymphocyte stimulation tests, which measure "how T cells are responding to an antigen." (Tr. 108-11 (citing Yukitoshi Takahaski et al., *Vaccination and Infection as Causative Factors in Japanese Patients with Rasmussen Syndrome: Molecular Mimicry and HLA Class I*, 13 CLINICAL & DEVELOPMENTAL IMMUNOLOGY 381 (2006) (Ex. 86)).) The identified sequence is part of a twenty-five amino acid protein segment of hemagglutinin shown to induce antibodies following a flu infection. (Ex. 69, pp. 5-6 (citing Niloufar Kavian et al., *Vaccination with ADCC Activating HA Peptide Epitopes Provides Partial Protection from Influenza Infection,* 38 VACCINE 5885 (2020) (Ex. 75)).) Dr. Steinman therefore concluded that the flu vaccine can "trigger an immune reaction to the Glutamate receptor, targeted in Rasmussen's [encephalitis]." (*Id.* at 7.)

Although Rasmussen's encephalitis is considered an ultra-rare orphan condition (Tr. 84), Dr. Steinman identified several case reports associating vaccinations with Rasmussen's encephalitis (*Id.* at 97). One such case report identified two patients who reported that they developed Rasmussen's encephalitis after vaccination. (*Id.* at 99-101 (citing Yukitoshi Takahashi et al., *Vaccination and Infection as Causative Factors in Japanese Patients with Rasmussen Syndrome: Molecular Mimicry and HLA Class I*, 13 CLINICAL & DEVELOPMENTAL IMMUNOLOGY 381 (2006) (Ex. 86)).) One patient developed seizures two months after vaccination, had MRI lesions on his frontal lobe, and "had autoimmune antibodies against glutamate receptor epsilon 2." (*Id.* at 100 (citing Takahashi et al., *supra*, at Ex. 86).) The second patient developed aseptic meningitis three weeks after receiving the MMR vaccine, and then developed seizures. (*Id.* at 100-01 (citing Takahashi et al., *supra*, at Ex. 86).)

Dr. Steinman acknowledged that the studies he identified linking the flu vaccine to Rasmussen's encephalitis also identify infection as a cause. (Tr. 112 (citing Takahashi, *supra*, at Ex. 85, p. 5, fig.5).) However, he asserted that E.M.'s physicians ruled out infection as a possible cause. (*Id.* at 112-13 (discussing Ex. 152), 122-25 (citing Ex. 139), 170-71 (citing Ex. 134, p. 1926).) He noted that E.M. did have a positive HSV IgM test; however, he explained that this test does not differentiate between HSV type 1 or type 2 and, when tested again for HSV using IgG, she was positive for HSV type 1, which is very common and is not necessarily evidence of an acute infection. (*Id.* at 114-16.) Instead, Dr. Steinman suggested that the positive HSV IgM results were possibly due to E.M's treatment with plasmapheresis. (*Id.* at 119.) Additionally, E.M.'s brain biopsy, which did find T cells, did not show any evidence of HSV. (*Id.* at 116-18 (discussing Ex. 152), 125-26 (discussing Ex. 139).) Nor did her CSF results. These results, according to Dr. Steinman, suggest that there is an inflammatory response in the brain; however, it is unlikely a result of an HSV infection. (*Id.* at 118.) Ultimately, Dr. Steinman opined that, based on her lab results, E.M. was infected with HSV at some point in her life, "but certainly not in her brain or in her CSF." (*Id.* at 120-21.)

With respect to timing, Dr. Steinman opined that between one to two days and eight weeks is "an acceptable time frame between vaccinations and onset of neuroinflammatory condition." (Tr. 162-63 (citing Lawrence B. Schonberger et al., *Guillain-Barre Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-1977*, 110 AM. J. EPIDEMIOLOGY 105 (1979) (Ex. 96)).) Dr. Steinman cited a review article that analyzed cases of inflammatory central nervous system conditions, including encephalitis, optic neuritis, and myelitis, following administration of various vaccines, including both the flu and HPV vaccine, and determined that onset occurred within days to around five months. (Tr. 164-65 (citing Dimitrios Karussis & Panayiota Petrou, *The Spectrum of Post-Vaccination Inflammatory CNS Demyelinating Syndromes*, 13 AUTOIMMUNITY REVS. 215, 218-19 (2014) (Ex. 42, pp. 4-5)).) He noted that E.M. received the HPV vaccine on July 20, 2015, and started experiencing visual disturbances approximately one month later, on August 15, 2015. (Ex. 23, p. 40; Tr. 79, 121-22, 185-88.) He further noted that petitioner began experiencing papilledema around September 15, 2015. (Ex. 23, p. 40.) According to

Dr. Steinman, this timeline "is consistent with the onset of neuroinflammation following vaccination." (Ex. 23, p. 40 (citing Til Menge et al., *Neuromyelitis Optica Following Human Papillomavirus Vaccination*, 79 NEUROLOGY 285 (2012) (Ex. 47); L. Bennetto & N. Scolding, *Inflammatory/Post-Infectious Encephalomyelitis*, 75 J. NEUROLOGY NEUROSURGERY & PSYCHIATRY (SUPP. 1) i22 (2004) (Ex. 58)); Tr. 169.)

Dr. Steinman further explained that E.M. received her flu vaccination on November 10, 2015. (Tr. 78.) He acknowledged that petitioner did not begin having seizures until December 9, 2015; however, he maintained that, "[i]n some patients, a prodromal period of mild hemiparesis or infrequent seizures might precede the onset of the acute stage by up to several years." (Ex. 23, p. 40 (quoting Varadkar et al., *supra*, at Ex. 49); Tr. 215-16.) He explained further that the lesions on E.M.'s MRI in September may have been evidence that something was "brewing" or "preclinical manifestations" of what would eventually become (but was not yet) Rasmussen's encephalitis. (Tr. 211, 216-18.) Nonetheless, Dr. Steinman opined that, in his opinion, the flu vaccine was a contributing factor in E.M.'s development of Rasmussen's encephalitis. (*Id.* at 218-19.) Dr. Steinman opined that onset of seizures beginning December 9, 2015, following a flu vaccination administered on November 10, 2015, constitutes an appropriate timeframe from which to infer causation. (Tr. 165-69 (citing Karussis & Petrou, *supra*, at Ex. 42; William Huynah et al., *Post-Vaccination Encephalomyelitis: Literature Review and Illustrative Case*, 15 J. CLINICAL NEUROSCI. 1315 (2008) (Ex. 98) (patient with bilateral optic neuropathies who developed ADEM three months after receipt of a flu vaccine); S. Vilain et al., *Encephalomyelitis and Bilateral Optic Perineuritis After Influenza Vaccination*, 277 BULLETIN SOCIETE BELGE D'OPHTALMOLOGIE 71 (2000) (Ex. 106) (patient who developed presumptive encephalomyelitis diagnosis, with symptoms that included headaches, urinary retention, bilateral optic disk swelling, and mild bilateral visual defect, five days after receiving a flu vaccination); Sabrina Ravaglia et al., *Post-Infectious and Post-Vaccinal Acute Disseminated Encephalomyelitis Occurring in the Same Patients*, 251 J. NEUROLOGY 1147 (2004) (Ex. 112) (two patients who suffered a relapse of post-infectious encephalomyelitis and myelitis roughly two weeks after receiving a flu vaccine); Paolo Pellegrino et al., *Acute Disseminated Encephalomyelitis Onset: Evaluation Based on Vaccine Adverse Events Reporting Systems*, 8 PLOS ONE e77766 (2013) (Ex. 93) (VAERS and EudraVigilance post-authorisation module data reveals that most patients developed ADEM between 2 and 30 days following flu or HPV vaccination, with some patients reporting even longer after vaccination)).)

ii. Jeffrey M. Silverman, M.D.

Petitioners also presented the opinion of Dr. Jeffrey M. Silverman. Dr. Silverman submitted one expert report and testified during the entitlement hearing. He was offered without objection as an expert in radiology.[24] (Ex. 68; Tr. 267.) Dr. Silverman reviewed

[24] Dr. Silverman is a board-certified radiologist. (Ex. 68, p. 1; Ex. 137, p. 3.) He received his medical degree from University of California San Diego School of Medicine, completed an internship in internal medicine at Cedars-Sinai Medical Center, and completed a residency in diagnostic radiology at Cedars-Sinai Medical Center. (Ex. 68, p. 1; Ex. 137, p. 2; Tr. 261.) He also completed a fellowship in

E.M.'s various brain MR scans, as well as her orbit MR scan, cervical spine MR scan, and head PET-CT. (Ex. 68, p. 2; Tr. 267.) In his report, Dr. Silverman offered three observations:

- E.M.'s September 25, 2015 MRI study "showed not only evidence of left optic neuritis and a few bilateral hyperintense nonspecific nonenhancing findings in the subcortical white matter" but also "a small volume of left temporal lobe abnormal signal on the T2 weighted and T2 weighted FLAIR sequences that does not have evidence of enhancement or restricted diffusion." (Ex. 68, p. 3.)

- E.M.'s December 29, 2015 MRI study showed "new abnormal signal and other areas of worsening abnormal signal in the brain." (*Id.*)

- "The abnormal findings have progressed (with areas of atrophy and gliosis) as reflected in the November 15, 2019 MR scan." (*Id*.)

During the hearing, Dr. Silverman expanded on these observations, presenting several images from the MRI studies and also addressing the significance of certain findings from an MRI conducted in the interim, on December 12, 2015. Pertinent to the analysis below, Dr. Silverman acknowledged that the left temporal lobe abnormality seen on the September 25, 2015 MRI was not visible on the December 12, 2015 MRI. (Tr. 282, 309.) However, he explained that inflammatory lesions can wax and wane over time, whereas an MRI is only a snapshot; that intervening treatment can be confounding; and that the technology used between the two scans differed significantly. (*Id.* at 282-83, 314-15, 572-91.) In effect, the September 25, 2015 MRI was more sensitive than the December 12, 2015 MRI. (*Id.* at 572-91.) In particular, the scanner used in September was 3 tesla with an echo train length of 1, whereas the scanner used on December 12 was 1.5 telsa with an echo train length of 14. (*Id.* at 578-79.) According to Dr. Silverman, these are meaningful differences that have "significant effects of image quality." The higher tesla improves the contrast between "signal" and "noise," and the shorter echo train reduces spatial blurring. (*Id*.) These differences will affect how conspicuous a lesion appears on the resulting imaging, meaning that the two scans are not an "apples to apples" comparison. (*Id.* at 580-81.) Thus, Dr. Silverman opines that the seeming disappearance of some of E.M.'s September lesions is actually due, at least in part, to the difference in MRI technology. (*Id.* at 581.) Additionally, he opines that E.M.'s MRIs, beginning with her September 25, 2015 MRI, showed a progression of inflammatory abnormalities predominantly on the left side. (*Id.* at 296.) According to Dr. Silverman, this opinion "mostly" agrees with the radiology reports within the medical records, except that the September 25, 2015 radiology report did not

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CT/Ultrasound/MRI Body Imaging with Special Emphasis in Cardiothoracic imaging at Cedars-Sinai Medical Center. (Ex. 68, p. 1; Tr. 262.) He has practiced as an attending physician since 1991. (Ex. 68, p. 1.) From 1995 to 2001, he served as the Director of Magnetic Resonance Imaging at Cedars-Sinai Medical Center. (Ex. 68, p. 1; Ex. 137, p. 11; Tr. 263.) He currently works as a Clinical Associate Professor of Radiology at the University of Southern California Keck School of Medicine. (Ex. 68, p. 1; Ex. 137, p. 10; Tr. 260.) Throughout his career, he has reviewed over 10,000 brain and spine MR scans. (Ex. 68, p. 1.) Additionally, he has authored multiple peer-reviewed articles and lectured on the specialty of MR imaging. (*Id.*; Ex. 137, pp. 12-28.)

separately identify the left temporal lobe abnormality identified by Dr. Silverman, though he suggests that it may have been implicitly included in the finding of "numerous scattered small foci of T2 hyperintensity." (*Id.* at 304-05 (discussing Ex. 8).) Dr. Silverman explained that, from a radiology perspective, the lesions are most likely inflammatory; however, determining whether they are demyelinating is a matter of clinical correlation. (*Id.* at 286-87, 300.)

b. Respondent's Experts

i. Jenny Linnoila, M.D., Ph.D.

Respondent offered an expert neurology opinion from Dr. Jenny Linnoila. Dr. Linnoila submitted three expert reports and testified at the entitlement hearing. She was offered without objection as an expert in neurology, neuroimmunology, and autoimmune neurology.[25] (Exs. C, F, H; Tr. 331.)

Dr. Linnoila opined that E.M. developed optic neuritis in the autumn of 2015. During the hearing, she noted that the timing of onset is unclear from the medical records, but ultimately placed onset in late August or early September. (Tr. 347-48, 463-64.) Because the specific findings of afferent papillary defect ("ADP") and red desaturation were not observed until her September 24, 2015 encounter, Dr. Linnoila opined that E.M.'s optic neuritis was initially "fairly mild" and reached its maximum severity after weeks, and around the time of her September 24, 2015 encounter. (Ex. C, pp. 6-7.) She opined that E.M. had a good clinical recovery following her steroid treatment. (*Id.* at 7-8.) She stressed that the optic neuritis had resolved clinically, according to patient report, by early November. (*Id.* at 7; Tr. 348-50.) During the hearing, she also testified that, based on E.M.'s December 12, 2015 MRI, the optic neuritis also resolved radiologically by that time. (Tr. 362-63.) In her initial report, however, she had opined that E.M.'s December 10, 2015 lumbar puncture, which showed improved but still elevated white blood cell count in her CSF, was consistent with still "resolving" optic neuritis. (Ex. C, p. 8 (citing Ex. 8, p. 542).)

Dr. Linnoila disagreed that the scattered lesions noted on E.M.'s September 25, 2015 MRI report were related to her optic neuritis, as they were appropriately characterized as non-specific. (Ex. C, p. 7 (citing Ex. 8, p. 742).) However, during the hearing, she agreed that a left temporal lobe lesion identified by Dr. Silverman, but not explicitly referenced in the radiology report, was associated with the optic neuritis. (Tr.

[25] Dr. Linnoila is a board-certified neurologist. (Ex. C, p. 2; Ex. D, p. 5; Tr. 321.) She received her medical degree and her Ph.D. in basic neuroscience and molecular pharmacology from the University of Pittsburgh in 2009 and 2007, respectively. (Ex. C, p. 1; Ex. D, p. 1; Tr. 318.) She completed a joint Harvard Neurology Residency Training Program at Massachusetts General Hospital and Brigham and Women's Hospital. (Ex. C, p. 1; Ex. D, p. 1.) Dr. Linnoila then completed a clinical fellowship in Autoimmune Neurology at the Mayo Clinic in Rochester, Minnesota. (Ex. C, p. 1; Ex. D, p. 1; Tr. 320.) After completing the fellowship, she returned to Massachusetts General Hospital to start a clinical practice in paraneoplastic and autoimmune neurology, as well as a research program focused on creating a rodent model of autoimmune encephalitis. (Ex. C, p. 1.) She has written several review articles and book chapters on autoimmune encephalitis, as well as peer-reviewed basic science and clinical research articles. (*Id.* at 2; Ex. D, pp. 6-8.)

426-27.) Thus, Dr. Linnoila agreed that E.M.'s optic neuritis constituted a broader demyelinating syndrome. (*Id.* at 567-68.) She stressed, however, that the left temporal lobe lesion was not evidenced on E.M.'s December 12, 2015 MRI, meaning that, in her opinion, it had resolved prior to that point, consistent with recovery due to E.M.'s steroid treatment for the optic neuritis.[26] (Tr. 420-27.)

Dr. Linnoila explained that, in a patient of E.M.'s age, inflammation and resulting demyelination is the most likely cause of optic neuritis. (Ex. C, p. 7.) She also agreed that MOG-related syndrome, a demyelinating syndrome, is among the causes of optic neuritis, as indicated by Dr. Steinman. (*Id.* at 10 (citing Chang & Pineles, *supra*, at Ex. C, Tab 8); Tr. 351.) In E.M.'s case, Dr. Linnoila opined that the optic neuritis is consistent with a demyelinating cause and, further, that "it is possible that her optic neuritis, in particular, could have been secondary to MOG-antibody-related disease." (Ex. C, pp. 10, 17 (citing Yael Hacohen & Brenda Banwell, *Treatment Approaches for MOG-Ab-Associated Demyelination in Children*, 21 CURRENT TREATMENT OPTIONS NEUROLOGY 1 (2019) (Ex. C, Tab 16)).) However, Dr. Linnoila does not agree that E.M.'s HPV vaccine caused her optic neuritis, stressing that linear sequence homology is insufficient to demonstrate molecular mimicry. (*Id.* at 11; Tr. 351.)

Dr. Linnoila further opined that E.M.'s condition from December of 2015 onward is best characterized as Rasmussen's encephalitis. Dr. Linnoila emphasized that Rasmussen's encephalitis is distinct from "autoimmune encephalitis," stressing that, in E.M.'s case, "testing for antibodies that are known to be associated with autoimmune encephalitis was negative." (Ex. C, p. 8 (citing Ex. 8, p. 1359).) Dr. Linnoila described Rasmussen's encephalitis as a "chronic, progressive condition of one-half of the brain," in which that half of the brain atrophies, causing seizures and neurological deficits. (Tr. 396-97.) On the other hand, autoimmune encephalitis causes alteration of mental status and seizures, focal findings on an MRI, or abnormalities in the spinal fluid. (*Id.* at 400-02 (citing Graus et al., *supra*, at Ex. 153).) Additionally, Dr. Linnoila explained that ADEM, which was also in E.M.'s differential diagnosis, causes large disseminated demyelinating lesions throughout the brain and spinal cord. (*Id.* at 403-04.) Dr. Linnoila concluded that E.M.'s subsequent neurological disorder "is most consistent with Rasmussen's encephalitis," not ADEM. (Ex C, p. 10; Tr. 352, 405.)

Dr. Linnoila confirmed that scientific literature does not document an association between optic neuritis and Rasmussen's encephalitis and noted that, although Dr. Steinman offered literature showing a link between uveitis and Rasmussen's encephalitis, uveitis is distinct from inflammation of the optic nerve. (Ex. C, p. 11; Tr. 381-83.) Specifically, a review published by Fauser et al. "concluded that patients who develop [Rasmussen's encephalitis] were not more likely to have a history of autoimmune disease than control patient." (Ex. H, p. 3 (citing Susanne Fauser et al., *Rasmussen Encephalitis: Predisposing Factors and Their Potential Role in Unilaterality*,

[26] During the hearing, petitioner's counsel questioned Dr. Linnoila's qualifications to opine on E.M.'s MRIs, given that she is not board eligible in diagnostic radiology nor had she completed any diagnostic radiology training. (Tr. 488-502.) Dr. Linnoila explained that she reads MRIs on a daily basis to treat her patients. (*Id.* at 551-53.)

63 EPILEPSIA 108 (2022) (Ex. H, Tab 4)).) During the hearing, Dr. Linnoila acknowledged that patients with Rasmussen's encephalitis often have "unilateral early acquired structural brain lesions" or facial autoimmune diseases that affect the skin or eye; however, she pointed out that E.M. did not track the course of the patients with early structural lesions, nor was optic neuritis one of the associated autoimmune diseases. (Tr. 529-31 (quoting Fauser et al., *supra*, at Ex. H, Tab 4, p. 10).) Thus, she disagreed that optic neuritis can lead to Rasmussen's encephalitis. (*Id.* at 352.)

Dr. Linnoila acknowledged that both conditions involve neuroinflammation; however, "neuroinflammation is found in many disorders of the brain that do not represent the same disease process." (Ex. H, p. 2 (citing Eduardo Candelario-Jalil et al., *Neuroinflammation, Stroke, Blood-Brain Barrier Dysfunction, and Imaging Modalities*, 53 STROKE 1473 (2022) (Ex. H, Tab 3); Mahmoud S. Alghamri et al., *Targeting Neuroinflammation in Brain Cancer: Uncovering Mechanisms, Pharmacological Targets, and Neuropharmaceutical Developments*, 12 FRONTERS PHARMACOLOGY 1 (2021) (Ex. H, Tab 1)).) She stressed that these two conditions are distinct in that optic neuritis is an autoimmune demyelinating condition that is responsive to treatment and Rasmussen's encephalitis is not.[27] (*Id.*; Ex. C, p. 11; Tr. 345.) However, during the hearing, while she again reiterated that Rasmussen's encephalitis was distinct from autoimmune encephalitis, she also acknowledged that Rasmussen's encephalitis can involve an autoimmune process and can be considered an immune mediated disease. (Tr. 343-45, 512-13.) Specifically, T cells in the brain evidence that such an autoimmune process is taking place. (*Id.* at 343-45.) She also acknowledged that a patient can have both a demyelinating condition and an autoimmune encephalitis at the same time. (*Id.* at 511-12.)

Dr. Linnoila explained that infections, and particularly the fevers associated with infections, can trigger Rasmussen's encephalitis. (Tr. 357 (citing Fauser et al., *supra*, at Ex. H, Tab 4).) She indicated that "autoimmune processes are often secondary or . . . triggered by some infectious process happening first, and then" the immune system warps and manifests as an autoimmune reaction. (*Id.* at 358-59.) Further, she described the infection as usually being the first event, followed by inflammation, and then leading to Rasmussen's encephalitis. (*Id.* at 360.) Dr. Linnoila opined that E.M.'s

[27] Dr. Linnoila explained Dr. Steinman's theory as being based on the presumption that Rasmussen's encephalitis and the associated epilepsy "are manifestations of an autoimmune disease." (Ex. C, p. 13 (quoting Ex. 23, p. 17).) However, Dr. Linnoila noted that the National Institute of Neurological Disorders and Stroke ("NINDS") definition of Rasmussen's encephalitis states that the condition "has features of an autoimmune disease," not that it is one. (Ex. C, p. 13.) Instead, she explained that "Rasmussen's encephalitis has been associated with T cell infiltration in the brains of patients"; however, it is "also associated with severe seizures, which themselves have been shown to cause immune cells to enter the brain," resulting in inflammation. (*Id.*) This inflammation then leads to more seizures, creating an inflammation-seizure cycle, which she explains is why these seizure disorders can be treated with anti-inflammatory medications, even though they are not autoimmune disorders. (Ex. C, p. 13.) She opined that because "it is difficult to separate the effect of seizures from the Rasmussen's encephalitis itself and Rasmussen's encephalitis is notoriously refractory to treatment," it is not solely an autoimmune neurogenic process. (Ex. C, p. 14 (citing Jenny Linnoila & Sean J. Pittock, *Autoantibody-Associated Central Nervous System Neurologic Disorders*, 36 SEMINARS NEUROLOGY 382 (2016) (Ex. C, Tab 14)).)

Rasmussen's encephalitis was most likely the results of a viral illness and fevers, not the flu vaccine. (Ex. H, p. 5.) She noted that, according to the EMTs, E.M. had a fever of 101.1 when she was evaluated in the ambulance. (Tr. 486. *But see id.* at 537-47 (cross-examination regarding the presence of fever).) Moreover, "E.M. initially tested positive for IgM antibodies for herpes simplex virus (HSV), which implies early infection." (Ex. H, p. 5 (citing Ex. 8, p. 1854); Tr. 506.) Dr. Linnoila acknowledged that even a positive IgM test could be positive for as many as 12 months and that E.M.'s biopsy showed no evidence of HSV; however, she noted that infections outside of the brain can have neurological consequences. (Tr. 510 (citing Ex. 134, p. 1341), 519-20, 553.) She further explained that, even if HSV was not the culprit, E.M. had reported a sore throat and some chills for two days before her seizure. (*Id.* at 559-61 (citing Exs. 14, 115).)

Dr. Linnoila explained that, apart from case reports, she was unable to find any literature that linked any vaccine to Rasmussen's encephalitis. (Tr. 340-41.) Additionally, she explained that the studies cited by petitioner do not conclusively link vaccinations and Rasmussen's encephalitis, and instead call for immunogenic studies to investigate the possible link. (*Id.* at 477-78 (citing Takahashi, *supra*, at Ex. 85, p. 3).) These studies, however, also report infection as a possible theoretical cause. (*Id.* (citing Takahashi, *supra*, at Ex. 85, p. 3).) Therefore, she opined that Rasmussen's encephalitis "developed after what was most likely a viral illness and low grade fevers, which preceded the development of seizures that were difficult to control and progressed overtime," which then led "to a cycle of inflammation, which can exacerbate circumstances by leading to a cycle of further seizures and inflammation." (Ex. C, p. 18; Ex. H, p. 5.) Dr. Linnoila later acknowledged that only about 15% of Rasmussen's encephalitis patients have a proceeding fever. (Tr. 529 (citing Fauser et al., *supra*, at Ex. H, Tab 4).)

Dr. Linnoila also concluded that E.M.'s Rasmussen's encephalitis occurred after her optic neuritis had resolved in October of 2015, and five months after the administration of the second HPV vaccine. Thus, she does not believe "that the timing for Rasmussen's encephalitis fits with an adverse event from E.M.'s second HPV shot." (Ex. C, pp. 16-17; Ex. F, p. 2.) When asked about a prodromal phase for Rasmussen's encephalitis, Dr. Linnoila explained that this is a general term that only means there is an initial symptom that may then develop into a syndrome. (Tr. 373-74.) She opined that a prodromal phase lasting three to four months would be extremely unlikely. (*Id.* at 468-69.) She explained that, if there was a prodrome in this case, it would encompass the fact that E.M. was not feeling well and had a fever before her seizure; it would not extend back to her optic neuritis. (*Id.* at 470-72.) Dr. Linnoila also acknowledged E.M.'s problems in math in the months prior to her seizures, but explained that, in her opinion, this is not evidence of her Rasmussen's encephalitis developing and, instead, may be a symptom of the steroids she was on for her optic neuritis. (*Id.* at 473.) Additionally, she noted that there is no MRI evidence in this case of Rasmussen's encephalitis beginning before E.M.'s December MRI. (*Id.* at 376-77.) Therefore, Dr. Linnoila explained that the first clinical event of petitioner's Rasmussen's encephalitis was her seizure. (*Id.* at 469-70.) She concludes that "[b]ased on the lack of a demonstrated link between optic

neuritis and Rasmussen's encephalitis . . . . as well as the timing of the initial seizures, it cannot be logically concluded that the vaccine more likely than not caused E.M.'s Rasmussen's encephalitis." (Ex. C, p. 17.) Dr. Linnoila acknowledged the case reports by Takahaski et al., which reported one patient developing Rasmussen's encephalitis two months after the Japanese encephalitis vaccine and another patient developing Rasmussen's encephalitis a year after the MMR vaccine, but explained that she "would not draw any conclusions from that data." (Tr. 480.)

ii. Dr. Christine McCusker, M.Sc., M.D.

Respondent's immunology expert, Dr. McCusker, submitted three expert reports and testified during the entitlement hearing. She was proffered, without objection, as an expert in pediatric immunology.[28] (Exs. A, E, G; Tr. 610.)

Dr. McCusker explained that "optic neuritis is characterized by sudden onset vision loss, usually unilateral, and associated with demyelination of the optic nerve." (Ex. A, p. 3.) She stated that the cause is unknown but noted that there is often "a history of an acute viral illness in the month preceding onset of symptoms leading to the suggestion that there may be an infectious trigger in this disease." (*Id.*) She acknowledged that vaccination "has also been temporally linked to onset of [optic neuritis]." (*Id.*) She further explained that Rasmussen's encephalitis "is a rare progressive disease, usually with childhood onset, characterized by hemispheric brain inflammation leading to, often unilateral, brain atrophy." (*Id.* at 4 (citing Tiziana Granata & Frederick Andermann, *Rasmussen Encephalitis*, 111 HANDBOOK CLINICAL NEUROLOGY 511 (2013) (Ex. A, Tab 7)).) Like optic neuritis, the cause of the disease is unknown, but Dr. McCusker noted that viral infection has been proposed as a trigger, especially because triggering of CD8+ve T cells that target astrocytes and neurons, which has been associated with Rasmussen's, is a sign of viral infection. (*Id.* (citing Granata & Andermann, *supra*, at Ex. A, Tab 7); Ex. E, p. 3 (citing Granata & Andermann, *supra*, at Ex. A, Tab 7); Ex. G, p. 4 (citing Granata & Andermann, *supra*, at Ex. A, Tab 7).) Dr. McCusker opined that optic neuritis and Rasmussen's encephalitis are immunologically different diseases that would require different immune responses. (Tr. 703-04.) Specifically, optic neuritis is caused by Th17 T cell inflammation, whereas the formation of cytotoxic T cells causes Rasmussen's encephalitis. (*Id.* at 704.) Usually, if a patient has two autoimmune conditions, Dr. McCusker testified that they "follow the same path." (*Id.* at 709.)

[28] Dr. Christine McCusker holds a Master of Science degree in molecular biology and a medical degree, both received from McMaster University in Ontario, Canada. (Ex. A, p. 1; Ex. B, p. 1; Tr. 601.) She is certified by the American Board of Pediatrics and by the Royal College of Physicians and Surgeons of Canada and by the College des Medecins du Quebec in both allergy and clinical immunology and pediatrics. (Ex. A, p. 1; Ex. B, p. 2; Tr. 605.) She currently serves as an associate professor of pediatric allergy and immunology at McGill University and as Division Director of Pediatric Allergy, Immunology, and Dermatology at the Montreal Children's Hospital. (Ex. A, p. 1; Ex. B, p. 3; Tr. 600, 603-04.) In her clinical capacity, Dr. McCusker sees an average of 50 to 120 children per week in allergy and clinical immunology and urgent care. (Ex. A, p. 2.) In her research capacity, she has submitted roughly 100 publications, primarily focused on immune response regulation. (Ex. B, pp. 20, 25-36; Ex. A, p. 1.)

Dr. McCusker stressed that there is no evidence that the HPV vaccine causes optic neuritis or encephalitis. She cited a study by Baxter et al., which found no increased frequency of optic neuritis within four to six weeks following vaccination. (Ex. A, p. 3 (citing Baxter et al., *supra*, at Ex. A, Tab 1); Ex. E, pp. 2-3; Ex. G, p. 5; Tr. 612-14, 618.) During the hearing, Dr. McCusker acknowledged that the Baxter et al. study reported that, while there were no statistically significant associations found between vaccines and optic neuritis, larger studies were needed to completely rule out associations. (Tr. 726 (citing Baxter et al., *supra*, at Ex. A, Tab 1, p. 3).) She also discussed a study by Liu et al., which examined the risk of autoimmune disorders, including optic neuritis, following the HPV vaccine. (Ex. A, p. 3 (citing Erin Y. Liu et al., *Quadrivalent Human Papillomavirus Vaccination in Girls and the Risk of Autoimmune Disorders: The Ontario Grade 8 HPV Vaccine Cohort Study*, 190 CANADIAN MED. ASS'N J. E648 (2018) (Ex. A, Tab 2)); Ex. G, p. 5.) Among almost 300,000 girls, the Liu et al. study found no increased frequency of demyelinating disease of the central nervous system following the HPV vaccination. (Ex. A, p. 3; Tr. 620-22.) Additionally, another study that "examined all codes for [optic neuritis] and compared the frequency of onset with HPV vaccination using data from 4.6 million individuals" found "no difference in frequency of [optic neuritis] following HPV vaccination." (Ex. A, p. 4 (citing Sridhar et al., *supra*, at Ex. A, Tab 4)); Tr. 624-25.) However, again, Dr. McCusker later acknowledged that the study called for additional larger studies to confirm their result. (Tr. 726-27 (citing Sridhar et al., *supra*, at Ex. A, Tab 4, p. 7).) Another study by Mouchet et al. found no significant association between the HPV vaccine and demyelinating diseases, including optic neuritis. (Ex. A, p. 4 (citing Julie Mouchet et al., *Human Papillomavirus Vaccine and Demyelinating Diseases—A Systematic Review and Meta-Analysis*, 132 PHARMACOLOGICAL RSCH. 108 (2018) (Ex. A, Tab 5)); Tr. 626-28.) Dr. McCusker also discussed a study by Miranda et al. which analyzed over two million girls who had received the HPV vaccine to see if there was any causal relationship between the HPV vaccine and autoimmune diseases. (Tr. 622-23 (citing Sara Miranda et al., *Human Papillomavirus Vaccination and Risk of Autoimmune Diseases: A Large Cohort Study of Over 2 Million Young Girls in France*, 35 VACCINE 4761 (2017) (Ex. A, Tab 3)); Ex. A, p. 3.) The study did not find an increased risk of optic neuritis, but did find an increased incidence of GBS. (Tr. 623 (citing Miranda et al., *supra*, at Ex. A, Tab 3).) While Dr. McCusker acknowledged that there have been cases demonstrating a temporal association between the HPV vaccine and optic neuritis, she stressed that no evidence supports a causal relationship. (Ex. A, p. 4; Tr. 614-19, 629.)

Regarding Dr. Steinman's theory that the HPV vaccine can cause Rasmussen's encephalitis via molecular mimicry, Dr. McCusker emphasized that, in the earliest stage of inflammation in patients with the condition, "there is the formation of microglial nodules with increase in expression of the innate immunity." (Ex. A, p. 5 (citing Anna R. Tröscher et al., *Microglial Nodules Provide the Environment for Pathogenic T Cells in Human Encephalitis*, 137 ACTA NEUROLPATHOLOGICA 619 (2019) (Ex. A, Tab 8)); Tr. 673-74.) However, "there is no evidence of T cells in the areas of these nodules although expression of chemokines involved in attracting [CD8+ve CTL] cells are increased."

(Ex. A, p. 5 (citing Tröscher et al., *supra*, at Ex. A, Tab 8).) During the intermediate stage of inflammation, Dr. McCusker explained that T cells infiltrate the area of the micronodules and form secondary nodules. (Ex. A, p. 5 (citing Tröscher et al., *supra*, at Ex. A, Tab 8); Tr. 674.) However, she noted, that the T cells do not just appear in the brain, and instead, must be called there. (Tr. 679-80.) At this stage, Dr. McCusker explained that cytokines are expressed, and initial neurodegeneration occurs. (Ex. A, p. 5.) In the acute stage, "there is extensive [CD8+ve CTL] cell infiltration with significant microglial cell activation and neurodegeneration." (Ex. A, p. 5 (citing Tröscher et al., *supra*, at Ex. A, Tab 8).) Dr. McCusker opined that Rasmussen's encephalitis "is initiated by increased expression of TLR3 and 7, usually increased in response to viral RNA, followed by T cell infiltration and cell death." (Ex. A, p. 5.) As support for her hypothesis, Dr. McCusker explains that viruses such as HPV, EBV, CMV, and HSV have been detected in the brain tissues of Rasmussen's encephalitis patients. (Ex. A, p. 5 (citing Shuai Chen et al., *Elevated Expression of Human Papillomavirus Antigen in Brain Tissue of Patients with Rasmussen's Encephalitis*, 126 EPILEPSY RSCH. 119 (2016) (Ex. 41)); Tr. 676 (citing Yao Zhang et al., *Expression of Human Cytomegalovirus Components in the Brain Tissues of Patients with Rasmussen's Encephalitis*, 32 VIROLOGICA SINICA 115 (2017) (Ex. G, Tab 9)).) Dr. McCusker theorized that, for the Rasmussen's encephalitis to be limited to one area of the brain, there must be an anatomical reason or the Rasmussen's encephalitis must be the result of a viral infection in that part of the brain. (Tr. 675.) Dr. McCusker noted that E.M. had evidence of an acute viral (HSV) infection at the time of her hospitalization. (Ex. A, p. 6 (citing Ex. 8, p. 1854).) Additionally, E.M. "had uni-hemisphere disease and showed no evidence of autoantibody formation and viral particles were not detected in the CNS." (*Id.*) Thus, Dr. McCusker opined that E.M. "first developed micronodules followed by T cell infiltration and onset of symptoms." (*Id.*) Had petitioner first developed T cell autoimmunity after the HPV vaccination as Dr. Steinman suggested, Dr. McCusker opined that petitioner would have bilateral disease. (*Id.* (citing Hania Kebir et al., *Humanized Mouse Model of Rasmussen's Encephalitis Supports the Immune-Mediated Hypothesis*, 128 J. CLINICAL INVESTIGATION 2000 (2018) (Ex. A, Tab 10)).)

Dr. McCusker noted that there are limitations with Dr. Steinman's use of BLAST searches to identify sequence homologies. (Ex. A, p. 6 (citing Christophe Benoist & Diane Mathis, *Autoimmunity Provoked by Infection: How Good Is the Case for T Cell Epitope Mimicry?*, 2 NATURE IMMUNOLOGY 797 (2001) (Ex. A, Tab 11)).) She noted that "Dr. Steinman failed to provide any control analysis showing no other sequence homology existed between the virus and other human proteins," nor did he analyze any other virus that may have infected" E.M. (*Id.*; Tr. 683-84.) Additionally, she explained that Dr. Steinman "is postulating antigenic mimicry for activation of CD8+ve T cells" without analyzing "the sequences for binding into class I major histocompatibility antigens (MHC)," which "is required . . . to determine if any of the homologous sequences are presentable to T cells via MHC." (Ex. A, p. 6.) Finally, she explained that Dr. Steinman would also need to analyze the MHC phenotype of E.M. "to determine if she bears the appropriate MHCs for binding and presenting the relevant peptides to T cells." (*Id.*) Dr. McCusker also noted that the criteria Dr. Steinman used to identify mimics is developed from studies performed on animals that do not "examine[]

sequences from human papilloma virus." (Ex. E, pp. 3-4 (citing Gautam et al., *supra*, at Ex. 51; Gautam et al., *supra*, at Ex. 52; Gautam et al., *supra*, at Ex. 53).) Additionally, Dr. McCusker noted that not all mimics are clinically relevant. (Tr. 669-70.)

Dr. McCusker performed her own BLAST search and highlighted that there is a high frequency of matches that fit Dr. Steinman's criteria, suggesting that "match frequencies occur as a product of chance and do not represent a biologically meaningful association." (Ex. A, p. 7 (citing Andre Silvanovich et al., *The Value of Short Amino Acid Sequence Matches for Prediction of Protein Allergenicity*, 90 TOXICOLOGICAL SCIS. 252 (2006) (Ex. 54)); Ex. G, p. 3).) She also performed a BLAST search for HSV, specifically due to E.M.'s IgM positivity and the fact that viruses have been proposed as a trigger for Rasmussen's encephalitis, and identified some homology. (Tr. 690-91.) Further, Dr. McCusker explained that T cells autoreactive to myelin basic protein have been found in patients with and without MS, suggesting "the presence of these autoreactive T cells are part of normal immunoregulation and do not necessarily participate in the development of disease." (Ex. A, p. 7 (citing Kohei Ota et al., *T-Cell Recognition of an Immuno-Dominant Myelin Basic Protein Epitope in Multiple Sclerosis*, 346 NATURE 183 (1990) (Ex. 56); M. Pette et al., *Myelin Basic Protein-Specific T Lymphocyte Lines from MS Patients and Healthy Individuals*, 40 NEUROLOGY 1770 (1990) (Ex. 57)).) Additionally, Dr. McCusker explained that the T cells identified by Dr. Steinman as responsible for E.M.'s condition, CD8+ve T cells "do not recognize proteins alone but rather they only identify proteins that have been picked up by MHC molecules," which "are used by the immune system to identify 'self.'" (*Id.*) Therefore, the identified protein sequences must be those that are identified by MHC molecules, which, as Dr. McCusker explained, is unaddressed by Dr. Steinman's BLAST searches. (Ex. A, p. 7; Ex. E, p. 5.)

In addressing Dr. Steinman's use of the Immune Epitope Data Base, Dr. McCusker explained that Dr. Steinman's criteria still do not identify any association between the molecular mimics he singles out and autoimmunity. (Ex. E, p. 4.) Dr. McCusker performed a similar analysis on six sequences from HSV and found that all of these sequences met Dr. Steinman's criteria. (*Id.* at 5.) However, there were also "multiple references for these sequences being implicated in autoimmune diseases for [three] of these sequences," unlike the sequences identified by Dr. Steinman. (*Id.* at 4-5.)

Dr. McCusker additionally challenged Dr. Steinman's theory that the flu vaccine can cause Rasmussen's encephalitis. (Ex. G.) Dr. McCusker questioned the relevance of a study by Kavian et al., noting that no patients suffered seizures caused by the influenza-specific antibodies and that no study shows the presence of NMDA-R antibodies in sera following the flu vaccine. (Ex. G, pp. 2-3 (citing Kavian et al., *supra*, at Ex. 75).) She emphasized that E.M. received five flu vaccines prior to the one at issue and "thus would have broad cross protective immunity to influenza." (*Id.* at 3 (citing Ex. 8, p. 1752).) She further stressed that E.M. "did not have any pathologically associated autoantibodies including NMDA-R despite extensive screening." (*Id.* (emphasis omitted).) While Dr. McCusker noted that several autoantibodies have been

identified in patients with Rasmussen's, she stressed that for "each autoantibody specificity is not consistently found." (*Id.*) She further noted that Rasmussen's encephalitis usually affects one hemisphere of the brain while proteins of identified autoantibodies are expressed bilaterally. (*Id.* at 3-4.) She concluded that this "suggest[s] that these autoantibodies are an epiphenomenon rather than a real pathological mechanism" in Rasmussen's encephalitis. (*Id.* at 4.) Finally, Dr. McCusker also noted that a study performed by Kawai et al. reported "no increased risk of encephalitis following influenza vaccine."[29] (*Id.* (citing Alison Tse Kawai et al., *Absence of Associations Between Influenza Vaccines and Increased Risks of Seizures, Guillain-Barré Syndrome, Encephalitis, or Anaphylaxis in the 2012-2013 Season*, 23 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 548 (2014) (Ex. G, Tab 12)).) Dr. McCusker also cited a study by Britton et al., where the "finding of infrequent varicella related encephalitis" suggested "that vaccination reduces the incidence of encephalitis in general." (Ex. G, p. 5 (citing Philip N. Britton et al., *Causes and Clinical Features of Childhood Encephalitis: A Multicenter, Prospective Cohort Study*, 70 CLINICAL INFECTIOUS DISEASES 2517 (2020) (Ex. G, Tab 4)).) During the hearing, Dr. McCusker discussed the Takahashi et al. article cited by Dr. Steinman and noted that the lymphocyte stimulation was an expected immune response to a flu vaccine. Without a control incorporating the flu vaccine and not the glutamate receptors, it is not possible to isolate the significance of the glutamate receptors. (Tr. 696-700.)

Dr. McCusker explained that if petitioner's HPV vaccine did cause her optic neuritis, which then resolved, it is unlikely that the immune system would then trigger the cytotoxic T cell response that occurs in Rasmussen's encephalitis. (Tr. 704-06.) Dr. McCusker noted that the HPV and flu vaccines were not live viruses and produced antibodies, not the cytotoxic T cells that lead to Rasmussen's encephalitis. (*Id.* at 676-78.) Instead, Dr. McCusker pointed out that viral infections are a known cause of Rasmussen's encephalitis and can elicit that needed T cell response. (*Id.* at 691-92.) In this case, Dr. McCusker interpreted E.M.'s IgG and IgM tests to indicate a primary infection that could have caused her Rasmussen's encephalitis. (*Id.* at 691, 739-40.) Additionally, she performed a BLAST search because HSV is occasionally found in biopsies of patients with Rasmussen's encephalitis. (*Id.* at 690.) Additionally, HSV can infect neurons. (*Id.* at 690-91.) During the hearing, Dr. McCusker acknowledged that E.M.'s CSF PCR test, her January 12, 2016 IgG and IgM tests, and biopsy were negative for HSV and confirmed that no viruses were found in E.M.'s central nervous system. (*Id.* at 721-23, 744, 755.)

Regarding timing, Dr. McCusker noted that E.M. had her first seizure 4.5 months after vaccination, when the HPV vaccination would have been cleared from her system. (Ex. A, p. 6; Tr. 676.) She also noted that E.M.'s first seizure occurred within 30 days of her flu vaccination. (Tr. 724.) Dr. McCusker cited an animal study that found seizure activity began within three weeks of infusion with cells from Rasmussen's encephalitis donors. (Ex. A, p. 6 (citing Kebir et al., *supra*, at Ex. A, Tab 10); Ex. G, p. 5.) Dr. McCusker did acknowledge that influenza infection has been linked to an increase in

[29] At the hearing, Dr. McCusker acknowledged that this study only analyzed individuals 21 days post-vaccination. (Tr. 729-30 (citing Kawai et al., *supra*, at Ex. G, Tab 12).)

the risk of encephalitis; however, there was no increased risk up to 180 days after flu vaccination. (Ex. G, p. 4 (citing Sara Ghaderi et al., *Encephalitis After Influenza and Vaccination: A Nationwide Population-Based Registry Study from Norway*, 2017 INT'L J. EPIDEMIOLOGY 1618 (2017) (Ex. G, Tab 11)).) Thus, Dr. McCusker concluded that the onset of petitioner's Rasmussen's encephalitis was not temporally associated with her HPV vaccination. (Ex. A, p. 6.)

VI. Analysis

This case presents an unusual and striking circumstance. E.M., by all measures, was an active and healthy twelve-year-old child in the summer of 2015, received her HPV vaccination in July, and subsequently suffered an uncommon syndrome of central nervous system demyelination inclusive of left-side optic neuritis and at least some degree of demyelination of the left side of the brain. The parties dispute whether that condition fully resolved, but she had a seemingly good clinical recovery. After completion of a steroid treatment, E.M. was doing well and was administered a flu vaccine in November, just three or so months after her HPV vaccination. Less than a month later, E.M. began experiencing seizures and successive MRIs showed a progressive condition on the left side of her brain. A brain biopsy confirmed a T-cell mediated encephalitis, consistent with Rasmussen's encephalitis, an ultra-rare neurologic condition distinct from her prior demyelinating condition. Although E.M.'s condition eventually plateaued, she cannot walk independently and will continue to have limited cognitive abilities, including a vocabulary of less than ten simple words and an inability to answer even somewhat complex questions. (Tr. 19-20.) E.M.'s mother testified that, around the time of her December hospitalization, E.M's final words before her cognitive ability declined were "Mama, I'm scared." (*Id.* at 52.)

Petitioners offer three potential explanations: E.M.'s entire presentation was caused by the HPV vaccine; E.M.'s HPV vaccine caused optic neuritis and her flu vaccine separately caused Rasmussen's encephalitis; or E.M. suffered optic neuritis caused by her HPV vaccine that acted as a first hit in the development of Rasmussen's encephalitis, with the flu vaccine additionally acting as a second hit, resulting in a significant aggravation. In all events, petitioners ultimately contend that, given the sequence of events, it is "inconceivable" that her vaccines were not factors in bringing about her condition. Petitioners' expert, Dr. Steinman, prefers the two-hit model of Rasmussen's encephalitis that supports a synergistic relationship between the two vaccinations. Respondent, by contrast, suggests that E.M.'s Rasmussen's encephalitis was caused solely by an HSV infection. Respondent does not suggest any alternative cause of E.M.'s optic neuritis. However, he stresses that optic neuritis and Rasmussen's encephalitis are too distinct to be causally related to one another. His experts, particularly Dr. McCusker, are content with the notion of lightning striking twice. (Tr. 706-08.)

To resolve the issues raised by the parties, the analysis that follows is divided into two parts. First, petitioners have preponderantly demonstrated that E.M.'s July 2015 HPV vaccine can and did cause her optic neuritis. Second, the evidence

preponderates in favor of a finding that E.M.'s optic neuritis was itself a cause of the later development of her Rasmussen's encephalitis, even though it would not have been the sole cause. This is a threshold finding with regard to petitioners' theory of causation vis-à-vis the flu vaccine; however, it also means that E.M.'s vaccine-caused optic neuritis was a proximate cause of her later Rasmussen's encephalitis. Thus, these findings are sufficient to entitle petitioners to compensation for E.M.'s complete post-vaccination clinical presentation regardless of whether her subsequent November 2015 flu vaccination is additionally implicated. Therefore, it is not necessary to reach petitioners' separate significant aggravation contention.

a. There is Preponderant Evidence that E.M. Suffered Optic Neuritis Caused-in-Fact by her HPV Vaccine (*Althen* Analysis with Respect to Optic Neuritis)

i. A medical theory of general causation is preponderantly supported (*Althen* prong one)

Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (citation omitted). To satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 548-49. However, petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)).

Dr. Steinman's theory as to how the HPV vaccine can cause optic neuritis is based on molecular mimicry[30] between a myelin protein, *i.e.*, MOG, and elements of the

[30] Molecular mimicry "is a generally accepted scientific principle, [but] mere invocation of the scientific term does not carry a petitioner's burden in a Program case." *Deshler v. Sec'y of Health & Human Servs*., No. 16-1070V, 2020 WL 4593162, at *20 (Fed. Cl. Spec. Mstr. July 1, 2020) (citing *Forrest v. Sec'y of Health & Human Servs.*, No. 14-1046V, 2019 WL 925495, at *3 (Fed. Cl. Spec. Mstr. Jan. 18, 2019)). This is because "the finding of sequence homology does not necessarily mean the similarity has significance to the immune system." *Tullio v. Sec'y of Health & Human Servs.*, No. 15-51V, 2019 WL 7580149, at *15 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), *mot. rev. denied*, 149 Fed. Cl. 448 (2020); *see also Caredio v. Sec'y of Health & Human Servs.*, No. 17-0079V, 2021 WL 4100294, at *31 (Fed. Cl. Spec. Mstr. July 30, 2021) (noting that "demonstration of homology alone is not enough to establish a preponderant causation theory" (emphases omitted)), *mot. for rev. denied*, No. 17-79V, 2021 WL 6058835 (Fed. Cl. Dec. 3, 2021). However, as noted above, petitioners in this program are not required to establish scientific certainty. Therefore, prior cases have expressed, with regard to the application of molecular mimicry, that "[t]he line must be drawn somewhere between speculation and certainty." *Brayboy v. Sec'y of Health & Human Servs.*, No. 15-183V, 2021 WL 4453146, at *19 (Fed. Cl. Spec. Mstr. Aug. 30, 2021). Thus, for example, in *Brayboy*, an omnibus proceeding addressing autoimmune premature ovarian insufficiency, the special master found it sufficient that the petitioners "identified cross-

HPV vaccine. (Ex. 23, pp. 20-29; Tr. 96-97.) Dr. Steinman explained that an autoimmune response to MOG is one of the main causes of optic neuritis (Ex. 23, p. 20 (citing Bettelli et al., *supra*, at Ex. 43; Steinman, *supra*, at Ex. 44; Kaneko et al., *supra*, at Ex. 45; Hacohen et al., *supra*, at Ex. 46), and respondent's neurology expert, Dr. Linnoila, agreed on respondent's behalf that MOG can be implicated as among the causal pathways to optic neuritis within related demyelinating disorders (Tr. 351). In fact, Dr. Linnoila agreed that it was possible that E.M.'s optic neuritis in particular was secondary to a MOG-antibody related disease. (Ex. C, p. 17 (citing Hacohen & Banwell, *supra*, at Ex. C, Tab 16)).)

From an immunologic perspective, Dr. McCusker cautioned on respondent's behalf that the pathophysiology of optic neuritis is not fully understood, but did agree that it is autoimmune and inflammatory. (Tr. 673, 704.) She further agreed that molecular mimicry is valid as a concept in general. (*Id.* at 717-18.) However, a significant issue for Dr. McCusker is "how does the vaccine in the arm get to the [central nervous system,] get to the pathology in the central nervous system, this is where I have trouble connecting the dots in this case." (*Id.* at 683.) Yet, Dr. Linnoila testified on respondent's behalf that "it's actually very common that there are autoimmune disorders that are triggered against the nervous system that didn't – that started or were triggered by a preceding infection that was somewhere else in the body." (*Id.* at 357.) Moreover, in discussing optic neuritis in her initial report, Dr. Linnoila cited approvingly to literature that accepts vaccination as a cause of optic neuritis, albeit without implicating the HPV vaccine specifically. (Ex. C, pp. 10, 17 (citing Chang & Pineles, *supra*, at Ex. C, Tab 8); *see also* Chang & Pineles, *supra*, at Ex. C, Tab 8, p. 2 (stating that "[o]ptic neuritis in children may be an idiopathic, isolated event; an autoimmune response to infection or immunization; or a manifestation of a systemic demyelinating disorder. In younger children, optic neuritis is more likely to occur following infection or vaccination, or as part of acute disseminated encephalomyelitis (ADEM).").) To that point, Dr. Steinman explained that, due to being adjuvanted, the Gardasil HPV vaccine produces a 40-fold more potent immune response than a natural viral HPV infection. (Ex. 23, pp. 19-20. (citing Souayah et al., *supra*, at Ex. 39).) For the specific HPV 16 and 18 components implicated by Dr. Steinman's theory, the immune response was 11-times higher than infection. (*Id.* (citing Souayah et al., *supra*, at Ex. 39).)

To demonstrate molecular mimicry between MOG proteins and the HPV vaccine, Dr. Steinman used a program called BLAST that allows for comparison of different peptide sequences. (Ex. 23, pp. 19-36.) Dr. Steinman has employed this type of search in many prior cases. It has been previously criticized. *E.g.*, *Forrest v. Sec'y of Health & Human Servs.*, No. 14-1046V, 2019 WL 925495, at *4-5 (Fed. Cl. Spec. Mstr. Jan. 28, 2019); *A.T. v. Sec'y of Health & Human Servs*., No. 16-393V, 2021 WL 6495241, at *24-25 (Fed. Cl. Spec. Mstr. Dec. 17, 2021). However, it has also been credited in some cases as contributing to the overall conclusion that petitioners have

reaction between components of the vaccine and proteins in the body that are directly responsible for the health and productivity of the organ at issue" and further expressed that requiring further steps, or "insisting on direct, testable evidence," would impermissibly heighten the petitioners' burden of proof. *Id*.

met their burden of proof under *Althen*. *E.M. v. Sec'y of Health & Human Servs*., No. 14-753V, 2021 WL 3477837, at *36-39 (Fed. Cl. Spec. Mstr. July 9, 2021); *White v. Sec'y of Health & Human Servs.*, No. 15-1521V, 2019 WL 7563239, at *24 (Fed. Cl. Spec. Mstr. Dec. 19, 2019). A significant limitation of Dr. Steinman's BLAST searches is that the results showing homology are not in themselves predictive of meaningful molecular mimics, having a high likelihood of showing matches that result merely from chance. *J.C. v. Sec'y of Health & Human Servs*., No. 17-69V, 2024 WL 3412625, at *18-19 (Fed. Cl. Spec. Mstr. May 16, 2024). Therefore, I have previously concluded that "the evidentiary value of these search results is limited and turns on whether the other evidence of record likewise supports a causal relationship between the vaccination and the type of injury at issue . . . . Without more, BLAST search results do not meet petitioner's preponderant burden of proof under *Althen* prong one." *Id*. at 19. The testimony elicited from respondent's immunology expert in this case is consistent with this conclusion. Dr. McCusker testified that, using BLAST, "I can find sequence homology to anything," but nonetheless also acknowledged that the tool could reasonably be used for "reverse engineering" a potentially significant match. (Tr. 687-88.)

Dr. Steinman compared MOG against the L1 protein from HPV 18 and HPV 16. (Ex. 23, pp. 24, 26.) He explained that the L1 protein is an external part of the virus and therefore is accessible to antibodies and T cells. (Tr. 88-89.) For HPV 18, he located a sequence with six of eleven identical amino acids. (Ex. 23, p. 25-26.) For HPV 16, he located a sequence with six of ten identical amino acids. (*Id*. at 27-28.) Dr. Steinman asserted that this degree of homology has been shown in peer-reviewed animal model studies as sufficient to trigger clinical neuroinflammation. (*Id.* at 36 (citing Gautam et al., *supra*, at Ex. 51; Gautam et al., *supra*, at Ex. 52; Gautam et al., *supra*, at Ex. 53).) Dr. McCusker disputed that short homologies of this type are predictive of any causally significant molecular mimicry and stressed the limitations of these animal models. (Ex. E, pp. 3-4; Ex. G, p. 3.) However, Dr. Steinman has also submitted a more recent publication by his own research group as proof of concept that a five out of twelve homology was sufficient to implicate the EBV virus as a cause of multiple sclerosis in humans. (Tr. 149-54 (Lanz et al., *supra*, at Ex. 71).) Dr. McCusker did not seek to rebut Dr. Steinman's reliance on the Lanz paper. Dr. Steinman also presented a study by Ufret-Vincenty et al. that specifically demonstrated in a mouse model of experimental autoimmune encephalomyelitis ("EAE"), an established model for the study of central nervous system demyelination, that peptides derived from the human papilloma virus were recognized by myelin basic protein-specific T cell clones from a multiple sclerosis patient, resulting in induction of autoimmune disease. (Ex. 23, pp 26-37; Rafael L. Ufret-Vincenty et al., *In Vitro Survival of Viral Antigen-Specific T Cells that Induce Experimental Autoimmunity Encephalomyelitis*, 188 J. EXPERIMENTAL MED. 1725 (1998) (Ex. 55).)

Dr. Steinman further cited a study by Sridhar et al. that purported to show that a second dose of Gardasil vaccine (as at issue in this case) carries an increased risk for the development of optic neuritis. (Tr. 135 (Sridhar et al., *supra*, at Ex. 40); Ex. 23, p. 20.) On respondent's behalf, Dr. McCusker opined that the Sridhar study overall does

not support a causal relationship between the HPV vaccine and optic neuritis after considering the secondary analysis, though she did acknowledge the study includes the specific finding relied upon by Dr. Steinman. (Tr. 726-27.) She also acknowledged that a separate study found an increased risk of GBS following HPV vaccination. (*Id.* at 727; Miranda et al., *supra*, at Ex. A, Tab 3.) Although GBS is a different condition, it is likewise viewed as a demyelinating condition in many cases.[31]

Thus, Dr. Steinman presented a sound and reliable opinion, based on the nature of optic neuritis (which literature filed by respondent agrees can be vaccine-caused), BLAST search results showing a proposed homology between HPV antigen and MOG, a mouse model showing HPV peptides being recognized by myelin basic protein-specific T cells, and other circumstantial evidence, supporting the theory that the HPV vaccine can cause optic neuritis. Additionally, E.M.'s treating physicians likewise felt that the HPV vaccine can cause optic neuritis. Specifically, both E.M.'s treating neuro-ophthalmologist (Dr. Digre) and infectious disease specialist (Dr. Thorell) cited within their assessments the fact that medical literature has reported demyelinating conditions, including optic neuritis and ADEM, as adverse reactions to the HPV vaccine (Ex. 7, pp. 66-67 (neuro-opthalmologist Dr. Digre); Ex. 134, pp. 1915-16 (infectious disease specialist Dr. Thorell)) before ultimately concluding that E.M. suffered vaccine-caused optic neuritis (Ex. 6, p. 17 (Dr. Digre diagnosing "Post vaccination opti" as of October 1, 2015); Ex. 139, p. 1 (Dr. Thorell reporting to VAERS that E.M. suffered optic neuritis following her second HPV vaccine). This further supports petitioners' *Althen* prong one showing. *See Patton v. Sec'y of Health & Human Servs*., 157 Fed. Cl. 159, 169 (2021) (finding that the diagnoses of the treating physicians that the petitioner suffered vaccine-caused brachial neuritis supported the reliability of petitioner's expert's theory of causation); *Capizzano*, 440 F.3d at 1326 (explaining that evidence used to satisfy one *Althen* prong can overlap to help satisfy another).

Additionally, though not controlling, it is worth noting that several special masters have concluded that the HPV vaccine can cause demyelinating central nervous system conditions, including optic neuritis. *Girardi v. Sec'y of Health & Human Servs.*, No. 17-181V, 2024 WL 4565887, at *27-30 (Fed. Cl. Spec. Mstr. Sept. 27, 2024) (finding the Cervarix HPV vaccine can trigger optic neuritis via molecular mimicry); *White v. Sec'y of Health & Human Servs.*, No. 15-1521V, 2019 WL 7563239, at *21-24 (Fed. Cl. Spec. Mstr. Dec. 19, 2019) (finding the Gardasil HPV vaccine can cause acute transverse myelitis via molecular mimicry); *B.A. v. Sec'y of Health & Human Servs.*, No. 11-51V, 2018 WL 6985218, at *31-32 (Fed. Cl. Spec. Mstr. Dec. 6, 2018) (finding preponderant evidence supporting a medical theory linking the HPV vaccine and ADEM). *But see Maciel v. Sec'y of Health & Human Servs.*, No. 15-362V, 2018 WL 6259230, at *26-28

[31] A potentially important distinction is that the demyelinating forms of GBS involve the peripheral nerves whereas optic neuritis is a condition affecting the central nervous system. In this case, however, respondent's neurology expert, Dr. Linnoila, herself invoked GBS as a prime example of how neurologic autoimmune conditions develop. (Tr. 357-58.) She invoked GBS in a discussion supporting her opinion that E.M.'s Rasmussen's encephalitis, also a central nervous system condition, could have been caused by an HSV infection even without entry of the HSV infection into the central nervous system. (*Id*.) Accordingly, both parties in this case present expert opinions that embrace GBS as usefully analogous despite involving the peripheral nervous system.

(Fed. Cl. Spec. Mstr. Oct. 12, 2018) (noting that, "[a]t a minimum, there is not enough reliable and persuasive evidence offered herein for me to find it plausible that the HPV vaccine could significantly aggravate the overall course of MS"); *Heddens v. Sec'y of Health & Human Servs.*, No. 15-734V, 2018 WL 5726991 (Fed. Cl. Spec. Mstr. Oct. 5, 2018) (concluding that petitioner has not preponderantly shown that the HPV vaccine can cause or significantly aggravate multiple sclerosis), *mot. for rev. denied*, 143 Fed. Cl. 193 (2019). And, notably, this includes cases accepting Dr. Steinman's specific contention in this case that peptide sequences from antigens in the HPV vaccine (as contained in both Gardasil and Cervarix) can cross-react with MOG proteins within myelin. *Girardi*, 2024 WL 4565887, at *28; *White*, 2019 WL 7563239, at *22.

A primary aspect of Dr. Linnoila's and Dr. McCusker's contrary view is that, despite a number of large studies having been conducted, no epidemiologic link has been uncovered between HPV vaccination and optic neuritis. The Federal Circuit has previously stressed that a petitioner is not obligated to prove a case with epidemiology. *Capizzano*, 440 F.3d at 1325. Yet, "[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory." *D'Tiole v. Sec'y of Health & Human Servs.*, 726 F. App'x 809, 811 (Fed. Cir. 2018). Accordingly, it is necessary to examine the epidemiology cited by respondent. In this case, the epidemiologic evidence, though entitled to some weight, does not significantly undermine Dr. Steinman's theory of causation.

Dr. McCusker cited Baxter et al., a case centered analysis that found no association between optic neuritis and any vaccine. (Baxter et al., *supra*, at Ex. A, Tab 1, p. 1.) The Baxter study began with the premise that "[t]he institute of Medicine observed that there was not sufficient evidence to either accept *or reject* the notion that vaccines are causally related to [optic neuritis]." (*Id.* (emphasis added).) Thus, the authors set out to examine numerous vaccinations administered in the Kaiser Permanente system for northern California, a population of 3.5 million members. (*Id*.) Focusing on this overall population figure, Dr. McCusker stressed the study as representing "a very big number when it comes to studies." (Tr. 617.) Importantly, however, the study only included 566,643 doses of HPV vaccine administered, which accounted for less than 3% of the vaccinations captured by the study. (Baxter et al., *supra*, at Ex. A, Tab 1, p. 2, tbl.1.) Thus, Dr. McCusker admitted upon cross-examination that the study authors had explicitly concluded that they could not rule out an increased risk of post-HPV vaccine optic neuritis without a larger study. (Tr. 726; Baxter et al., *supra*, at Ex. A, Tab 1, p. 3.) Dr. McCusker added, "that's why more studies have been done and published." (Tr. 726.) However, among the studies she additionally cited, Liu et al. did not match the Baxter study for size. Liu et al. was a cohort study of 290,939 HPV vaccine-eligible girls, of which 180,819 girls received at least one vaccine dose and 681 incident cases of autoimmune disorders were diagnosed. (Liu et al., *supra*, at Ex. A, Tab 2, p. 3.) This was as self-controlled series, meaning each subject was their own control. (*Id*. at 2.) Sixty-seven cases of optic neuritis were examined. (*Id*. at 5, tbl.1.)

Miranda et al. did exceed the size of the Baxter study, having examined 842,120 HPV-vaccinated girls. (Miranda et al., *supra*, at Ex. A, Tab 3, p. 3.) However, this study did not address optic neuritis separately (assessing central nervous system demyelinating conditions collectively)[32] and did not completely exonerate the HPV vaccine as a cause of autoimmune demyelination, given that it did detect an increased risk of post-HPV vaccination GBS, as noted above. (*Id.*) Dr. McCusker also cited a meta-analysis by Mouchet et al., which she characterized as applying a "rigorous" literature review. (Tr. 626; Mouchet et al., *supra*, at Ex. A, Tab 5.) She stated that Mouchet stands for the proposition that, "not just statistically speaking, but massively statistically speaking," there is no evidence that the HPV vaccine causes optic neuritis. (Tr. 628.) Looking at the study's specific discussion of optic neuritis, the authors identify six studies with risk estimates for optic neuritis. (Mouchet et al., *supra*, Ex. A, Tab 5, p. 7.) However, among those six studies are Baxter et al., in which the authors confirmed they could not rule out all increased risk of post-HPV vaccination optic neuritis, and Sridhar et al., which, as discussed above, included one specific finding of increased risk of optic neuritis after a second dose of HPV vaccine, i.e., the dose at issue in this case. (*Id.* at 4, 7.) For a third study, the authors explicitly note that, due to study flaws, "it should be interpreted with caution." (*Id*. at 3.) Thus, Miranda et al. and Mouchet et al. are not strong evidence.

In light of all of the above, and considering the record as a whole, there is preponderant evidence on this record that the HPV vaccine can cause optic neuritis.

ii. A logical sequence of cause and effect and an appropriate temporal relationship preponderantly support specific causation (*Althen* prongs two and three)

Having shown that the HPV vaccine can cause optic neuritis, petitioners must also establish that it did cause optic neuritis in this specific case. *Pafford*, 451 F.3d at 1356. This aspect of petitioners' *prima facie* showing is generally broken down into two further questions pursuant to *Althen* prongs two and three. The second *Althen* prong requires proof of a logical sequence of cause and effect usually supported by facts derived from a vaccinee's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1278. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* at 1281. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

[32] This is a potential issue because central nervous system demyelinating disorders have differing presentations and/or prevalence. *See, e.g. Doles v. Sec'y of Health & Human Servs*., No. 17-642V, 2022 WL 3229286, at *26-27 (Fed. Cl. Spec. Mstr. June 24, 2022) (quoting a review article by Mailand and Frederiksen explaining that a limitation in epidemiologic study of multiple sclerosis includes delay in diagnosis and significant variation in symptom presentation), *vacated on other grounds*, 163 Fed. Cl. 726 (2022).

E.M. received the second dose of her HPV vaccine on July 20, 2015 and subsequently developed optic neuritis in mid-August, roughly or close to a month after vaccination. A mid-August onset of optic neuritis is preponderantly supported based on review of the complete medical records. (Ex. 5, p. 2 (routine eye exam with optometrist of May 9, 2015 negative for any pathology and finding only myopia); Ex. 4, pp. 6-7 (no complaints recorded at July 20, 2015 encounter for second HPV vaccination); Ex. 5, p. 3 (return encounter with optometrist noting as of September 15, 2015, "one month" of symptoms later diagnosed as optic neuritis, placing onset in mid-August); Ex. 6, p. 1 (ophthalmology encounter noting onset of symptoms "[t]owards the end of summer," consistent with a mid-August onset); Ex. 8, p. 668 (neurology consultation recording as of October 8, 2015, a history of symptoms beginning "a couple months ago," potentially consistent with an August onset, and noting the normal eye exam in May).) The Federal Circuit has held that contemporaneous medical records are to be given significant weight because "the records contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. With proper treatment hanging in the balance, accuracy has an extra premium. These records are also generally contemporaneous to the medical events." *Cucuras,* 993 F.2d at 1528. Petitioners' testimony further supports a mid-August onset of optic neuritis. Mr. Marsh testified that E.M. began showing discomfort with her eye around mid-August of 2015. (Tr. 13.) Mrs. Marsh testified that E.M.'s eye problems began one month before her appointment with Dr. Beagley, likewise placing onset around mid-August. (*Id.* at 31.)

Nonetheless, respondent argues that several records place the onset of E.M.'s optic neuritis before she received the second dose of her HPV vaccine. (ECF No. 128, pp. 26-27.) In particular, on September 24, 2015, E.M.'s neuro-ophthalmologist, Dr. Digre, recorded that the duration of E.M.'s symptoms of optic neuritis was "3 months," which would place onset in June. (Ex. 6, p. 5.) However, the same record indicates in the history of present illness that the symptoms began "in July." (*Id*.) Thus, the history provided within this encounter reccord is internally inconsistent and in referencing a July onset does not clearly place onset prior to the July 20, 2015 vaccination.[33] Moreover, this history is in contrast to the earlier treatment records and stands alone in placing onset in June or July. Additionally, on December 12, 2015, E.M. underwent a neurology consultation during which it was noted that E.M. developed black spots with progressive tunnel vision in Spring of 2015. (Ex. 8, p. 477.) However, this consult took place six months after E.M.'s vaccination, and, as explained above, more contemporaneous records support a mid-August onset. Moreover, E.M.'s essentially normal eye exam from May of 2015 is in tension with onset occurring in the Spring of 2015. Ultimately, both of respondent's experts agreed that E.M.'s symptoms began after her vaccination. (Tr. 347-48, 361 (Dr. Linnoila indicating onset is unclear but agreeing it occurred after

[33] The two notations can potentially be harmonized if one were to conclude that the reference to "3 months" merely means that E.M.'s optic neuritis had to that point spanned three calendar months, *i.e.* beginning in July and continuing throughout August and into September. It should be noted that Dr. Digre did at a later encounter opine that E.M. was suffering post-vaccination optic neuritis (Ex. 6, p. 17) without specifically revisiting the timing of onset (*Id*. at 14). Accordingly, it would be illogical to interpret Dr. Digre's records as indicating she was under the impression that onset of the optic neuritis occurred prior to the vaccination.

the July 20, 2015 vaccination); Tr. 724-25 (Dr. McCusker acknowledged that there is some equivocation within the record with regards to timing, but placed onset of E.M.'s optic neuritis between one to two months after vaccination).)

There is preponderant evidence on this record that onset of a central nervous system demyelinating condition, such as optic neuritis, occurring approximately one-month post vaccination constitutes a medically acceptable temporal relationship. (Tr. 162-65; Ex. 23, p. 40; Karussis & Petrou, *supra*, at Ex. 42, p. 5, tbl.2 (identifying optic neuritis occurring 10 days to five months post-HPV vaccination); Pellegrino et al., *supra*, at Ex. 93, p. 3, tbl.1 (finding a majority of post-vaccination ADEM cases arose between 2-30 days post-vaccination); Huynah et al., *supra*, at Ex. 98, pp. 7-8 (patient presenting with bilateral optic neuropathies three weeks after flu vaccination developed ADEM three months after vaccination); Vilain et al., *supra*, at Ex. 106, p. 2 (patient with presumptive diagnosis of encephalomyelitis with bilateral optic perineuritis caused by influenza vaccination who developed symptoms five days after receiving his vaccine); Schonberger et al., *supra*, at Ex. 96, p. 1 (finding elevated risk of post-vaccination GBS "primarily" within five weeks). Prior program cases have often concluded that 2-42 days is an appropriate interval for post-vaccination onset of demyelinating conditions. *See e.g.*, *Girardi*, 2024 WL 4565887, at *32-33 (noting that a timeframe of 3-42 days has been accepted in cases involving peripheral and central nervous system diseases and finding as medically acceptable a 38-day onset of post-HPV vaccination optic neuritis); *Day v. Sec'y of Health & Human Servs.*, No. 12-630V, 2015 WL 8028393, at *21-23 (Fed. Cl. Spec. Mstr. Nov. 13, 2015) (finding a primary risk interval of 5-28 days and a secondary risk interval of 2-42 days persuasive with regards to post-vaccinal neurological disorders in a case involving post-HPV vaccination neuromyelitis optica); *Koller v. Sec'y of Health & Human Servs.*, No. 16-439V, 2021 WL 5027947, at *22-23 (Fed. Cl. Spec. Mstr. Oct. 8, 2021) (accepting a timeframe of 2-34 days for onset of GBS following Prevnar 13 vaccination); *Giannetta v. Sec'y of Health & Human Servs.*, No. 13-215V, 2017 WL 4249946, at *24-25 (Fed. Cl. Spec. Mstr. Sept. 1, 2017) (finding an onset with 42-47 days is an acceptable timeframe for onset of multiple sclerosis following Menactra vaccination); *Brancheau v. Sec'y of Health & Human Servs.*, No. 21-1209V, 2024 WL 1619606, at *23-26 (Fed. Cl. Spec. Mstr. Mar. 21, 2024) (noting the onset period for a Table Injury of GBS following flu vaccination is 3-42 days). Thus, a causal inference supporting vaccine causation is medically reasonable in this case based on the preponderantly established date of onset.

Following his review of E.M.'s medical history, Dr. Steinman has opined on petitioners' behalf that E.M.'s optic neuritis was caused by her July 20, 2015 HPV vaccination. (Ex. 23, p. 41.) As a neuroimmunologist, he is qualified to render that opinion. (*Id.* at 1 (noting that Dr. Steinman has cared for "hundreds of adults and children with various forms of inflammatory neuropathy," including optic neuritis).) Although respondent's neurology expert, Dr. Linnoila, reached the opposite conclusion, it is difficult to separate that opinion from her opinion regarding petitioner's theory of general causation with respect to optic neuritis. Dr. Linnoila did not raise any specific aspect of E.M.'s own clinical history as being incompatible with petitioner's proffered theory, which has been accepted as preponderantly demonstrated. Apart from

opposition under *Althen* prong one, the only issue respondent raises with respect to whether E.M.'s own clinical presentation of optic neuritis could have been vaccine caused is his assertion that onset of the condition pre-dated her July 20, 2015 HPV vaccination, which is unpersuasive for the reasons discussed above.[34] (ECF No. 128, pp. 26-28.) Respondent has not argued that E.M.'s optic neuritis was due to any factor unrelated to her vaccination. (*Id.* at 28-30.)

Indeed, E.M. was evaluated by a neuro-opthalmologist and an infectious disease specialist, both of whom felt E.M.'s history was potentially indicative of HPV-vaccine caused optic neuritis. (Ex. 6, p. 17 (neuro-opthalmologist Dr. Digre diagnosing "Post vaccination opti" as of October 1, 2015); Ex. 7, p. 66-67 (Dr. Digre writing that post-vaccination optic neuritis is to be considered as a diagnosis of exclusion, given that "[t]here have been reports of post HPV vaccination causing optic neuritis"); Ex. 134, p. 1915-16 (Dr. Thorell signing off as of January 16, 2016, on a consultation explaining that "[a] very rare ADEM/adverse immunization reaction to HPV has been reported in a few case studies and is also being entertained in light of the temporal relationship of her acquiring [optic] neuritis a few weeks after her second HPV vaccine," further noting that "autoimmune vis infection etiologies seem the most likely working differential at this point" and that a VAERS report was filed); Ex. 139, p. 3 (Dr. Thorell reporting to VAERS that E.M. suffered optic neuritis following her second HPV vaccine). Respondent challenges the validity of Dr. Thorell's VAERS report as it pertains to E.M.'s broader, longer-term condition, mainly because Dr. Thorell still suspected ADEM, but does not directly address Dr. Thorell's separate identification of a vaccine-related optic neuritis.[35] (ECF No. 128, pp. 21-25.)

Accordingly, petitioners have preponderantly demonstrated that onset of E.M.'s optic neuritis occurred during a post-vaccination timeframe from which vaccine causation can be inferred and also that a logical sequence of cause and effect, supported by both expert and treater medical opinion, supports the conclusion that E.M.'s HPV vaccine did cause of her optic neuritis.

[34] Though respondent argues onset pre-dated the vaccination, respondent does also seek to further cloud the question of onset by raising the fact that Dr. Thorell's VAERS submission indicated that E.M.'s optic neuritis occurred 6-7 weeks following her vaccination. (ECF No. 128, pp. 22, 24.) Dr. Thorell's VAERS report does not outweigh the contemporaneous treatment records. But in any event, a six-week onset would not be incompatible with a causal inference as explained above.

[35] Respondent contends that "[t]he Court of Federal Claims has repeatedly upheld special masters' decisions to give little weight to VAERS reports as evidence of causation." (ECF No. 128, n. 7.) However, this is misleading. What respondent cites are examples wherein special masters have rejected attempts to cull data from the VAERS database regarding other purportedly vaccine-injured individuals to support their claim. This is generally viewed as an unreliable approach because VAERS is a passive surveillance system and anyone can file a VAERS report. However, these concerns are irrelevant here. Dr. Thorell's VAERS submission is a detailed first-hand accounting of her reasoning, as E.M.'s treating physician, as to why a vaccine adverse event may be implicated in this very case.

b. There is Preponderant Evidence that E.M.'s Optic Neuritis was a But For Cause and Substantial Contributing Factor in the Development of her Subsequent Rasmussen's Encephalitis

Having established that E.M.'s optic neuritis was vaccine-caused, a key additional question necessary to a full resolution of this case is what – if any – relationship exists between E.M.'s optic neuritis and her subsequently occurring Rasmussen's encephalitis. Petitioners contend that they "have established that more likely than not the HPV vaccine caused [E.M.]'s Optic Neuritis. At the time [E.M.] received the influenza vaccine on November 10, 2015, she was suffering from Optic Neuritis. Thereafter, within thirty (30) days, her seizures began, which eventually were diagnosed as Rasmussen's Encephalitis. This supports the two-hit theory of Rasmussen's Encephalitis." (ECF No. 129, p. 32.) Thus, they suggest that "[i]t is inconceivable that [E.M.], thirty (30) days after the HPV vaccination, had an onset of Optic Neuritis and then thirty (30) days after her influenza vaccination had an onset of her seizures without the vaccine(s) being a substantial factor in her illness." (*Id.* at 32-33.)

Respondent likewise stresses that "[i]n an attempt to connect all the vaccine and all the theories, Dr. Steinman postulates that E.M.'s optic neuritis never resolved, and in fact led to the Rasmussen's Encephalitis." (ECF No. 128, p. 26.) Yet, respondent maintains that "E.M. suffered from two different entities – optic neuritis and Rasmussen's Encephalitis." (*Id*. at. 22.) And, moreover, "optic neuritis is not a feature of Rasmussen's Encephalitis." (*Id*.) Petitioners explain, however, that they "have never contended that optic neuritis itself caused or led to [E.M.]'s Rasmussen's Encephalitis." (ECF No. 129, p. 19.) Instead, they assert that the "HPV vaccine caused [E.M.]'s optic neuritis and brain inflammation. The autoimmune condition was present at the time of [E.M.]'s flu vaccination. The flu vaccination was the second hit which caused [E.M.]'s seizures." (*Id*. at 22.) In other words, the parties agree that E.M.'s Rasmussen's encephalitis is not merely an extension of her optic neuritis, given that they are distinct conditions; however, petitioners nonetheless argue that E.M.'s preexisting brain inflammation and autoimmunity due to her optic neuritis were causal factors contributing, with the addition of a second hit, to the development of her Rasmussen's encephalitis.

The two-hit model of Rasmussen's encephalitis proffered by petitioners, and preferred by their expert, Dr. Steinman, is distinct from the separately advanced alternative hypothesis that E.M.'s two vaccines each acted separately to cause two separate injuries. It seeks to place E.M.'s initial autoimmune injury as a first-hit, meaning that, despite not being the sole cause of her Rasmussen's encephalitis, the optic neuritis was a but for cause and substantial contributing factor in the development of the condition. Accordingly, any finding in petitioners' favor vis-à-vis the flu vaccination based on the two-hit model of Rasmussen's encephalitis would necessarily encompass a threshold finding that the Rasmussen's encephalitis was caused, at least in part, by the optic neuritis. Yet, because petitioners have demonstrated that the optic neuritis was vaccine caused, this same finding is sufficient to bring E.M.'s Rasmussen's

encephalitis under the umbrella of her compensable HPV vaccine-related optic neuritis claim, mooting any need to actually determine what constituted the second hit leading to her Rasmussen's encephalitis. In that regard, petitioners' amended petition, while additionally alleging a causal role for E.M.'s flu vaccination, explicitly preserved the allegation that the HPV vaccine causally contributed to the development of E.M.'s Rasmussen's encephalitis.[36] (ECF No. 59, p. 15.)

This is consistent with the standard adopted by the Federal Circuit in *Shyface vs. Secretary of Health & Human Services*, 165 F.3d 1344 (Fed. Cir. 1999). In *Shyface*, a child had died from respiratory failure brought about by a high fever along with dehydration and an infection. *Id*. at 1345. The petitioners argued that a prior vaccination was a proximate cause of the death because it had caused the fever that in turn contributed to the death. Respondent countered, however, that the infection was the principal cause of the death. *Id.* at 1345-46. The Federal Circuit held that the vaccine was a proximate cause of the death, explaining that, under the tort principles of proximate causation applicable to the Vaccine Act, petitioners are only obligated to demonstrate that the vaccine is both a "but for" cause and a "substantial contributing factor" in any alleged injury, rather than the sole cause. *Id*. at 1352. The Circuit further explained that, when concurrent causes are at issue, a petitioner may demonstrate the vaccine to have been a substantial contributing factor when it can be demonstrated that there is a causal theory connecting the vaccine and the injury, as well as a logical sequence of cause and effect showing that the vaccine was the reason for the injury, *i.e.*, a showing consistent with the *Althen* test. *Id*. at 1352-53. Whereas the *Shyface* petitioners alleged that vaccination caused a fever that in turn contributed to a subsequent death due to multiple causes, here petitioners allege the vaccine at issue caused optic neuritis that in turn contributed to development of Rasmussen's encephalitis, which they contend resulted from multiple causes.

Moreover, compensable injuries within this program encompass complications and residual effects of an initially vaccine-caused injury. § 300aa-11(c)(1)(D)(i). A complication is a disease or morbid process that co-occurs in the same patient as a result of another disease, without being an essential part of that disease. *Wright v. Sec'y of Health & Human Servs*., 22 F.4th 999, 1006 (Fed. Cir. 2022). In determining whether a complication is the result of an initially vaccine-caused condition, the same tort principles as adopted by the *Shyface* court are used. *Id.* at 1005. Thus, it is sufficient that a vaccine injury be both a but for cause and substantial contributing factor in bringing about a complication, even without necessarily being a predominant factor.

[36] As discussed below, the expert testimony in this case was clear in debating the potential interrelationship between Rasmussen's encephalitis and preceding optic neuritis; however, the parties' post hearing briefs were less helpful on this point in that they tended to gloss over this threshold question in favor of jumping straight to their respective arguments regarding the viability of the flu vaccine as the proposed second-hit within the multi-hit model of Rasmussen's encephalitis. (ECF Nos. 127-29.) *See Sword v. U.S*., 44 Fed. Cl. 183, 187 (1999) (explaining that "[n]o judge or jury can be forced to accept or reject an expert's opinion or a party's theory at face value. To require such a choice in this context is to neglect the Special Master's duty to 'vigorously and diligently investigate the factual elements' underlying the petition.").

Id. (citing *Shyface*, 165 F.3d at 1352). Under this standard, E.M.'s Rasmussen's encephalitis can be conceived of as a complication or sequela of her optic neuritis, *i.e.*, a co-occuring, but causally related, disease that cannot be said to be a part of the optic neuritis itself.

Accordingly, consistent with *Shyface*, the three-part *Althen* test will be applied to determine whether E.M.'s Rasmussen's encephalitis is causally related to her optic neuritis. As a result of that analysis, there is preponderant evidence that (1) optic neuritis can be a promoting factor in the development of Rasmussen's encephalitis (*Althen* prong one), (2) the timing of the course of events supports a causal inference that the optic neuritis contributed to the Rasmussen's encephalitis in E.M.'s case (*Althen* prong three), and (3) there is a logical sequence of cause and effect implicating E.M.'s optic neuritis in the development of her Rasmussen's encephalitis (*Althen* prong two). The last of these points encompasses a finding that respondent is unpersuasive in contending that an HSV infection, if implicated, would constitute the sole cause of the Rasmussen's encephalitis to the exclusion of the optic neuritis. Accordingly, there is preponderant evidence that E.M.'s Rasmussen's encephalitis is causally related to her prior optic neuritis and that her entire post-HPV vaccine presentation therefore constitutes a compensable injury.

i. <u>There is preponderant evidence that optic neuritis can causally contribute to Rasmussen's encephalitis as a predisposing or promoting factor (*Althen* prong one)</u>

Respondent's experts stress that optic neuritis and Rasmussen's encephalitis represent two distinct disease processes and therefore cannot reasonably be viewed as a single entity stemming from a single cause. (Tr. 352, 472, 704-08; Ex. C, pp. 11-12.) Dr. Steinman explained during the hearing, however, that it is nonetheless scientifically or medically reasonable to consider E.M.'s optic neuritis as a contributor to the development of the autoimmune process that led to her later Rasmussen's encephalitis, suggesting that two-hits involved "two anatomic levels." (Tr. 211-14.) Thus, he opined that, while it is also potentially reasonable to suggest that E.M.'s HPV and flu vaccines caused two separate injuries, the most likely scenario is that, as a result of a second hit, such as the later flu vaccine, the optic neuritis lesions "exploded into what we call Rasmussen's [encephalitis]." (*Id.* at 214.) Thus, he opined that both the HPV vaccine-caused optic neuritis lesions and the subsequent "hit" together culminated in the Rasmussen's encephalitis. (*Id*.) This explanation is persuasive as a theory, especially (but not only) in light of the literature filed by respondent. As explained above, petitioners must present a legally probable, but not necessarily scientifically certain, theory of causation based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548-49.

Dr. Linnoila introduced into the record of this case a paper by Fauser et al. (Susanne Fauser et al., *Rasmussen Encephalitis: Predisposing Factors and Their Potential Role in Unilaterality*, 63 EPILEPSIA 108 (2022) (Ex. H, Tab. 4).) Dr. Linnoila endorsed this paper as the work of a research group headed by Christian Bien, who she

identifies as "a world's expert" in Rasmussen's encephalitis. (Ex. H, p. 3.) Dr. Linnoila cited the Fauser paper for the proposition that there is no "general, nonspecific autoimmune predisposition" for Rasmussen's encephalitis. (*Id.* (quoting Fauser et al., *supra*, at Ex. H, Tab 4).) Consistent with Dr. Steinman's opinion, however, Fauser et al. indicate that pre-existing ipsilateral brain pathology[37] is compatible with a multi-hit pathogenesis for Rasmussen's encephalitis. (Fauser et al., *supra*, at Ex. H, Tab 4, p. 10.) While this pathology is often noted in the context of pre- or perinatal structural abnormalities, the authors observed broadly that Rasmussen's encephalitis may constitute a form of secondary autoimmune encephalitis that requires acquired comorbidities to disrupt the blood brain barrier and even suggested that incidental ipsilateral pathology findings have been tentatively interpreted as part of the multistage pathogenesis of Rasmussen's encephalitis. (*Id*. at 10-11.) Thus, they characterize pre-existing ipsilateral lesions as "promotive" of a "multiple hit" cascade that could also include subsequent febrile infection.[38] (*Id*. at 6.)

Furthermore, Dr. McCusker likewise explained on respondent's behalf that the T cells implicated in the development of Rasmussen's encephalitis must somehow be "invited" into the central nervous system. (Tr. 679-80.) Citing Tröscher et al., she opined that the T cells in Rasmussen's encephalitis act as responders, rather than initiators of disease. (*Id*. at 673-75 (citing Anna R. Tröscher et al., *Microglial Nodules Provide the Environment for Pathogenic T Cells in Human Encephalitis*, 137 ACTA NEUROPATHOLOGICA 619 (2019) (Ex. G, Tab 7)).) Thus, in order for the T cells that cause Rasmussen's encephalitis to attack the brain in the characteristic uni-hemisphere pattern, some form of anatomic change or infectious nidus must already be at work in the affected portion of the brain. (*Id*. at 675; Tröscher et al., *supra*, at Ex. G, Tab 7; *see also* Fauser et al., *supra*, at Ex. H, Tab 4, p. 10 (explaining that a subset of Rasmussen's encephalitis patients had one-sided early brain lesions or facial autoimmune lesions prior to onset of Rasmussen's encephalitis); Orsini et al., *supra*, at Ex. G, Tab 7, p. 4 (explaining that "studies performed on brain tissue, cerebrospinal fluid and blood from patients with [Rasmussen's encephalitis] demonstrated that the T-cells infiltrating the brain tissue expand from discrete precursor T-cells, supporting the theory of immune activation against a single, unidentified, antigen").)[39] Therefore, regardless

[37] Ipsilateral means "situated on, pertaining to, or affecting the same side." *Ipsilateral*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=26077 (last visited Feb. 10, 2025). As discussed further below, Dr. Linnoila agreed during the hearing that E.M.'s own optic neuritis constituted a broader syndrome of demyelination inclusive of a left hemisphere temporal lobe lesion (Tr. 567), the same hemisphere implicated as affected by the Rasmussen's encephalitis.

[38] Although much of petitioners' briefing focuses on the separate question of whether the flu vaccine can be implicated as the second hit, petitioners do specifically argue in their post-hearing submissions that respondent's filing of the Fauser paper supports Dr. Steinman's two-hit theory for the development of Rasmussen's encephalitis. (ECF No. 129, p. 12.)

[39] Both Dr. McCusker's testimony and the medical literature of record are broadly enough stated that petitioners cannot reasonably be tasked with demonstrating the actual antigen-presenting characteristics of a preexisting lesion. "Despite the identification of different pathogens in the brain tissue of patients with [Rasmussen's encephalitis], an association between the disease and a specific pathogen has not yet been identified." (A. Orsini et al., *Rasmussen's Encephalitis: From Immune Pathogenesis Towards*

of the fact that optic neuritis and Rasmussen's encephalitis involve distinct autoimmune pathways, Dr. McCusker's testimony, as well as the Fauser and Tröscher articles, support a causal role for a pre-existing brain abnormality or lesion in the development of Rasmussen's encephalitis. And, despite Dr. McCusker's overall conclusion against a causal relationship, this also substantiates Dr. Steinman's multi-hit explanation for Rasmussen's encephalitis. (*E.g.*, Fauser et al., *supra*, at Ex H, Tab 4, p. 10 ("We suggest a multihit model for the development of [Rasmussen's encephalitis], with early lesions, facial autoimmunity, or febrile onset being predisposing factors."); Tr. 213-14 (Dr. Steinman confirming during the hearing that his two-hit conceptualization withstands the assumption that the optic neuritis and Rasmussen's encephalitis are two separate disease processes).)

Dr. Steinman further explained that Rasmussen's encephalitis also involves an autoimmune process in which an initial T-cell driven response ultimately leads to the development of autoantibodies against glutamate receptors, either GLuR3 or GluRε2,[40] rendering it a form of autoimmune encephalitis.[41] (Tr. 137, 777-78; Ex. 50.) In that

Targeted-Therapy, 81 SEIZURE: EUR. J. EPILEPSY 76 (2020) (Ex. G, Tab 2, p. 4).) However, to the extent Dr. McCusker hypothesizes a role for an antigen-presenting nidus in particular, petitioner has filed literature demonstrating that elevated expression of HPV antigen has been found in the brain tissue of Rasmussen's encephalitis patients. (Chen et al., *supra*, at Ex. 41.) Petitioners' theory of vaccine-causation for E.M.'s optic neuritis, as discussed above, would not suggest that HPV antigen was itself present in E.M.'s brain tissue; however, the literature filed by both parties suggests that "the main infiltrating T-lymphocyte population in [Rasmussen's encephalitis] was likely explained *from a few precursor T-cells* that responded to discrete antigenic epitopes." (*Id.* at 1 (emphasis added); *see also* Orsini et al., *supra*, at Ex. G, Tab 2, p. 4 ("T-cells infiltrating the brain tissue expand from discrete precursor *T-cells* . . . ." (emphasis added)). In that regard, Dr. Steinman has purported to show molecular mimicry both between HPV antigen and MOG, as implicated in optic neuritis, as well as between HPV antigen and the glutamate receptor antibodies implicated in Rasmussen's encephalitis, at the T cell level. (Tr. 131-36.) Accordingly, while it is not necessary to reach this question, Dr. Steinman has at least raised the prospect that the T cells that are implicated in the development of E.M.'s optic neuritis, as a result of being implicated as responsive to molecular mimics of HPV antigen, could likewise be causally significant to the Rasmussen's encephalitis.

[40] Dr. Steinman suggests that GluRε2, which forms the basis of his theory implicating the flu vaccine, is better supported by the literature, though he notes that both types of receptor have been described in the literature. (Ex. 23, pp. 21, 28-36; Tr. 96, 137.)

[41] Respondent strenuously argues that Rasmussen's encephalitis cannot be equated to autoimmune encephalitis. (ECF No. 128, pp. 6-8.) Despite acknowledging that Rasmussen's encephalitis does result from T-cell autoimmunity (Tr 338, 343-44, 512), Dr. Linnoila opined that Rasmussen's encephalitis is not equivalent to "autoimmune encephalitis," which she explained is a distinct clinical entity with its own diagnostic criteria. (Ex. C, p. 10; Tr. 343-45, 354-56, 405, 512-13.) However, Dr. Steinman was persuasive in explaining that the literature cited by Dr. Linnoila, mainly Graus et al., identifies Rasmussen's encephalitis as a subset of autoimmune encephalitis. (Tr. 777-78 (citing Graus et al., *supra,* at Ex. 153, pp. 17-18, 31).) Graus et al. explain that the diagnostic criteria for autoimmune encephalitis is merely a "syndrome-based diagnostic approach" to a category of non-infectious encephalatides, rather than constituting definitive evidence of a distinct pathophysiology. (Graus et al., *supra*, at Ex. 153, pp. 1-2.) Thus, the authors note that, while Rasmussen's encephalitis has a different clinical presentation, the underlying autoimmune basis overlaps with autoimmune encephalitis. (*Id*. at 4.) Therefore, the distinction between autoimmune encephalitis and Rasmussen's encephalitis diagnostic criteria, as drawn by respondent, is primarily relevant to diagnosis, treatment, and prognosis (Tr. 513), and is less useful as a means of otherwise separating out the relative import of specific etiologies.

regard, respondent has filed literature explaining that at least one type of autoimmune encephalitis, namely NMDA receptor encephalitis,[42] is known to present as an "overlap syndrome" with demyelinating syndromes such as optic neuritis. (Bradshaw & Linnoila, *supra*, at Ex. C, Tab 5, p. 10.) The Graus et al. article, first cited by Dr. Linnoila during the hearing and later filed into evidence by petitioner, explains:

> About 4% of patients with anti-NMDA receptor encephalitis develop two different syndromes that can occur separately or simultaneously. Each syndrome is related to a distinct pathogenic mechanism, such as anti-NMDA receptor encephalitis along with MOG-related or aquaporin 4 (AQP4)-related syndromes . . . . In practice, physicians should be aware that a demyelinating disorder can present as an autoimmune encephalitis disorder, and that overlapping syndromes can occur. Patients with a demyelinating disorder and atypical features (eg, dyskinesias or prominent psychiatric manifestations) or patients with anti-NMDA receptor encephalitis with atypical features (eg, optic neuritis or demyelination on MRI) should be comprehensively studied for coexisting disorders, rather than being classified as having an expansion of the spectrum of a single disease.

(Graus et al., *supra*, at Ex. 153, pp. 14-15 (internal footnote omitted).) Consistent with the above explanation by Graus et al., Dr. Linnoila cautions that it is still unknown

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Moreover, Dr. Linnoila's opinion distinguishing the two conditions is based in part on the fact that she does not necessarily accept as established the specific theory, as cited by Dr. Steinman, that glutamate receptors act as targets of autoantibody attack in Rasmussen's encephalitis. (Ex. C, p. 12.) However, this amounts to a search for scientific certainty. Dr. Steinman's invocation of this theory is supported by medical literature establishing that it is considered among the viable theories of causation for Rasmussen's encephalitis. For example, literature filed by Dr. McCusker explains that "experimental studies underlined that also both humeral and innate immunity plays a role in the pathogenesis of [Rasmussen's encephalitis], even if their mechanism has yet to be fully elucidated." (Orsini et al., *supra*, at Ex. G, Tab 2, p. 4.) Thus, Graus et al. address Rasmussen's encephalitis under the heading of conditions "at the frontier of autoimmune encephalitis." (Graus et al., *supra*, at Ex. 153, p. 31.) The parties argue extensively in their post-hearing briefs about whether the treating physicians' focus on autoimmune encephalitis constituted a critical misdiagnosis in E.M.'s case. (*See* ECF No. 127, pp. 6-8; ECF No. 128, p. 8 & n.3; ECF No. 129, pp. 12-14.) However, while the treating physicians often listed autoimmune encephalitis and Rasmussen's encephalitis separately among their differential diagnoses, there are notations in the medical records confirming that the treating neurology team approached autoimmune encephalitis as a broader diagnosis, potentially encompassing of Rasmussen's encephalitis, rather than a mutually exclusive diagnosis. (*E.g.*, Ex. 8, p. 1965 (Dr. Sweeney, an autoimmune neurology fellow, discussing "autoimmune encephalitis with a similar phenotype . . . sometimes termed Rasmussen's encephalitis" and noting that antibodies including GLuR3 and NMDA and others have been identified in some patients, though are negative in E.M.'s case); Ex. 8, p. 1825 (diagnosing "[p]robable autoimmune encephalopathy/encephalitis, features suggestive of Rasmussen's encephalitis, with prior optic neuritis").)

[42] GluRε2 and GluR3 are part of a family of central nervous system receptors that also includes N-methyl-D-aspartate (NMDA) receptors. (Takahashi et al., *supra*, at Ex. 50, p. 2.) According to Dr. Steinman, GluRε2 is an "NMDA-type" receptor. (Tr. 137-38.) As Dr. Linnoila explains, NMDA receptor antibodies are the most common antibody identified in patients with autoimmune encephalitis. (*Id.* at 401.) However, the NMDA antibodies in NMDA receptor encephalitis target different NMDA subunits as compared to the GluRε2 antibodies. (Ex. C, p. 12-13.)

whether the demyelinating conditions involved in overlap syndromes have any causal connection to the co-occurring encephalitis. (Tr. 378-81.) However, the fact that the medical community recognizes "overlap syndrome" as an identifiable entity at a minimum counsels against treating the presence of the two conditions at issue as mere coincidence even as they remain different disease processes. In that regard, Fauser et al., citing GluR3 antibodies, does specifically posit that the glutamate receptor antibody theory of Rasmussen's encephalitis autoimmunity, as discussed by Dr. Steinman, is considered compatible with the multi-hit model of Rasmussen's encephalitis. (Fauser et al., *supra*, at Ex. H, Tab 4, p. 10.)

Furthermore, Fauser et al., though cautioning against a "general, nonspecific autoimmune predisposition" to Rasmussen's encephalitis, explain that certain prior autoimmune conditions affecting one side of the face, including scleroderma en coup de sabre,[43] uveitis,[44] or chorioretinitis,[45] have been identified as predisposing factors in the development of Rasmussen's encephalitis. (*Id.* at 6-7, 10.) Petitioners have likewise filed case reports of uveitis preceding Rasmussen's encephalitis. (Harvey et al., *supra,* at Ex. 33; Fukuda et al., *supra,* at Ex. 34.) Although optic neuritis is not specifically identified by Fauser et al., it is likewise an inflammatory autoimmune condition that can present unilaterally, albeit affecting the optic nerve, rather than the iris or retina as in uveitis or chorioretinitis, respectively.[46] (Baxter et al., *supra*, at Ex. A, Tab 1, p. 1; *see*

[43] Patients with scleroderma en coup de sabre experience a linear lesion of hardening and thickening skin affecting the frontal or frontoparietal area of the forehead and scalp. *Scleroderma*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=45002 (last visited Feb. 12, 2025); *Coup de sabre*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=67318 (last visited Feb. 12, 2025).

[44] Uveitis is an inflammation of part or all of the uvea, which commonly involves the other tunics of the eye (*i.e.*, sclera, cornea, and retina). *Uveitis*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=52355 (last visited Feb. 12, 2025). The uvea is the vascular coat of the eye that is comprised of the choroid, the ciliary body, and the iris. *Uvea*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=52354 (last visited Feb. 12, 2025); *Tunica vasculosa bulbi*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=115933 (last visited Feb. 12, 2025).

[45] Chorioretinitis involves inflammation of choroid and retina. *Chorioretinitis*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=9589 (last visited Feb. 12, 2025).

[46] It should be noted, however, that the retina is continuous with the optic nerve and does contain neurons. *Retina*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=43499 (last visited Feb. 12, 2025). The choroid, in particular, as affected in chorioretinitis, is a thin, vascular coating of the eyeball that permits nerve conduction from the optic nerve to the anterior structures of the eye. *Choroid*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=9593 (last visited Feb. 12, 2025). In E.M.'s case, she had confirmed optic disk swelling and papilledema (Ex. 5, p. 3; Ex. 6, p. 9), suggesting that her optic neuritis had an intraocular component, rather than merely being retrobulbar (*i.e.*, affecting the nerve behind the eye). *Intraocular neuritis*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=92511 (last visited Feb. 12, 2025); *Papilitis*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=36676 (last visited Feb. 12, 2025); *Retrobulbar neuritis*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=92527 (last visited Feb. 12, 2025).

also Granata & Andermann, *supra*, at Ex. A, Tab 7, p. 6 (hypothesizing more broadly that "[t]he possibility that a peripheral noxious agent may enter the brain and induce chronic inflammatory damage is raised by the few reports of [Rasmussen's encephalitis] associated with unilateral uveitis and choriorenretinitis").) And, interestingly, Fauser et al. suggest that facial autoimmunity may be of particular significance in cases of teenage onset of Rasmussen's encephalitis as compared to the more typical earlier childhood onset.[47] (Fauser et al., *supra*, at Ex. H, Tab 4, p. 10.)

Dr. Linnoila stressed that optic neuritis is distinct from the types of autoimmunity otherwise implicated as predisposing to Rasmussen's encephalitis in that it is demyelinating; however, it is inflammatory like the other conditions identified by Fauser et al. and, when asked to explain the relationship between inflammation and demyelination, Dr. Linnoila testified that the demyelination in optic neuritis is simply one consequence of inflammation. (Tr. 378-83.) Accordingly, this difference does not readily distinguish optic neuritis from the other forms of unilateral facial autoinflammation that have been shown to predispose patients to Rasmussen's encephalitis, especially given that demyelinating conditions are otherwise known to "overlap" with autoimmune encephalitis. Nothing in the Fauser et al. paper suggests optic neuritis is incompatible with the authors' observations. Fauser et al. observed broadly that "11 patients with facial autoimmune diseases also had their skin or eye affected on the side later intracranially affected by [Rasmussen's encephalitis]," phrasing that is broad enough to encompass intraocular optic neuritis. (Fauser et al., *supra*, at Ex. H, Tab 4, p. 10.) And, in fact, Fauser et al. do separately purport to refute the notion that several other autoimmune conditions – not including any demyelinating conditions – are predisposing to Rasmussen's encephalitis. (*Id.*)

Ultimately, Dr. McCusker testified that, because the two conditions at issue in this case require two different types of immune response, it is more reasonable based on what we know about these conditions to conclude that "[l]ightning struck twice" than to conclude that two pathophysiologically different conditions could be interrelated. (Tr. 703-08.)[48] However, this is not persuasive in light of the above. Fauser et al. specifically suggest, consistent with Dr. Steinman's opinion, that their findings are compatible with the idea that Rasmussen's encephalitis requires an "interaction of different pathogenic mechanism[s] as a prerequisite for a subsequent immunopathological reaction." (Fauser et al., *supra*, at Ex. H, Tab 4, p. 10.) In particular, they suggest that preceding ipsilateral pathology may act as the "lateralizing element" that explains the uni-hemispheric presentation of Rasmussen's encephalitis.

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[47] At twelve years of age, E.M. was beyond the typical childhood onset age of six to ten years on average. (Orsini et al., *supra*, at Ex. G, Tab 2, p. 1 (noting the mean age at presentation of Rasmussen's encephalitis is between six and eight years); Fauser et al., *supra*, at Ex. H, Tab 4, p. 4 (recording an average age at onset, based on the 244 Rasmussen's encephalitis patients studied, was ten years).)

[48] In addition to what is discussed throughout this section, it should also be noted that this reasoning was based in part on Dr. McCusker's assumption that E.M.'s optic neuritis had entirely resolved prior to the development of her Rasmussen's encephalitis. (Tr. 705-06.) However, this is not preponderantly supported for the reasons discussed in the next section.

(*Id*.) And, although Dr. Linnoila maintained that there is no basis for extending the Fauser group's research to include optic neuritis specifically, she indicated that she otherwise had no dispute with the multi-hit model of Rasmussen's encephalitis as explained by Fauser, et al. (Tr. 530-31.)

Moreover, all of the opining experts in this case have stressed that Rasmussen's encephalitis is an ultra-rare or "extremely rare" condition. (Tr. 83-84, 249-51, 336-39, 556, 732; Ex. A, p. 4.) Dr. Steinman characterized it as an "ultra orphan" disease, meaning that it is far less studied than other more common conditions. (Tr. 83-84.) In that context, it would impermissibly heighten petitioners' burden of proof to require direct evidence from literature of this unique combination of conditions – a somewhat rare neurologic condition (affecting 1 per 500,000 children) followed by an ultra-rare neurologic condition (affecting 1-2 per 10,000,000 children) – when the available literature otherwise (1) correlates demyelinating conditions with autoimmune encephalitis, (2) also separately correlates pre-existing ipsilateral facial autoinflammation affecting the eye with Rasmussen's encephalitis in particular, and (3) proposes a multi-hit model of Rasmussen's encephalitis that attributes a causal role to both pre-existing brain lesion(s) and autoimmunity affecting the face and eyes. Given the rarity of the condition, these three points represent clear circumstantial evidence supportive of a legally probable theory of causation. Petitioners are obligated only to present a sound and reliable, legally probable, causal explanation and are not required to present directly supporting medical literature. *Andreu*, 569 F.3d at 1378-79 (finding the special master erred in requiring conclusive evidence in the medical literature and citing *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 593 (1993), as explaining that "[s]ome propositions, moreover, are too particular, too new, or of too limited interest to be published"); *Althen*, 418 F.3d at 1280 (observing that requiring medical literature prevents the use of circumstantial evidence and contravenes "the purpose of the Vaccine Act's preponderance standard[, which] is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body"); *but see also Caves v. Sec'y of Health & Human Servs*., 100 Fed. Cl. 119, 143 (2011) (noting that [t]he standard of proof does not operate as a sliding scale that varies depending upon the quantity and quality of the scientific evidence that is available"), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012).

Accordingly, there is preponderant evidence on this record that optic neuritis, especially when associated with additional brain lesion(s), can be a substantial contributing factor in, and but for cause of, the later development of ipsilateral Rasmussen's encephalitis.

ii. <u>There is preponderant evidence that the latency between E.M.'s optic neuritis and Rasmussen's encephalitis is compatible with a causal inference (*Althen* prong three)</u>

Under *Althen* prong three, petitioners must demonstrate a "medically-acceptable temporal relationship." *Althen*, 418 F.3d at 1281. This showing is informed by the theory presented under *Althen* prong one. Accordingly, the question to be addressed

under *Althen* prong three is whether the time between the development of E.M.'s optic neuritis and the later development of her Rasmussen's encephalitis accords with what would be expected if the former were to be considered among the causes of the latter, consistent with the above-discussed multi-hit understanding of Rasmussen's encephalitis.

Pertinent among the hypotheses for the cause(s) of Rasmussen's encephalitis is the theory that Rasmussen's encephalitis is a para-infectious autoimmune process wherein a T-cell mediated immune response evolves into antibody-driven autoimmunity, most likely to glutamate receptors. (Takahashi et al., *supra*, at Ex. 86, p. 3.) As explained above, Fauser et al. felt the multi-hit model of Rasmussen's encephalitis is consistent with this understanding. (Fauser et al., *supra*, at Ex. H, Tab 4, p. 10.) In that regard, a review of Japanese patients found that 38.2% of patients had a preceding infection. (Takahashi et al., *supra*, at Ex. 86, p. 4, tbl.1.) One third of patients had an infection within one month of onset. (*Id.* at p. 1.) Dr. McCusker further stressed that it is theorized that Rasmussen's encephalitis develops in three stages (identified as stages 0-2), with the inflammatory T-cell response beginning at stage one, after microglia in the brain have already become antigen-presenting in the context of pathologic changes that begin in "stage zero." (Tr. 673-74; Tröscher, *supra*, at Ex. G, Tab 7, p. 2.) Stage one constitutes a prodromal period of disease progression and stage two represents the acute phase of the condition. (Tröscher, *supra*, at Ex. G, Tab 7, p. 2.) The prodromal phase, which sees intermittent symptoms, can last for months. (Orsini et al., *supra*, at Ex. G, Tab 2, p. 1.)[49] Takahashi further examined Rasmussen's encephalitis by analyzing glutamate (GluRε2) autoantibodies from 46 patients with acute encephalitis or encephalopathy. (Takahashi, *supra*, Ex. 85, p. 6.) He categorized the patients as having either "localized" or "widespread" encephalitis based on the initial clinical symptoms. (*Id*.) Patients with localized encephalitis had psychiatric symptoms, solitary seizures, and/or mildly impaired consciousness, and then later developed more severe conditions with a convulsive status. (*Id*.) According to Takahashi, the presence of autoantibodies against GluRε2 in the cerebral spinal fluid is significantly correlated to the onset of epilepsy in cases of widespread encephalitis. (*Id*.) Among those initially presenting with localized encephalitis, antibodies tended to appear between 0-60 days after the first onset of neurologic symptoms. (*Id.* at 7.) All of this together indicates that it can take up to about 30-60 days for the expected immune response to culminate in the acute phase of Rasmussen's encephalitis.

In this case, the parties' experts agree that E.M.'s first seizure on December 9, 2015, heralded the acute phase of her Rasmussen's encephalitis. (Tr. 216, 377.) Accordingly, if E.M.'s optic neuritis is to be considered causally relevant as the source of the initiating precursor T cells (at stage zero), then this autoinflammation should have been ongoing until at least sometime between mid-October to mid-November, about 30-60 days prior to onset of the acute phase of E.M.'s Rasmussen's encephalitis, occurring

[49] The articles by Orsini et al. and Tröscher et al. discuss the same underlying disease process but use different labels when discussing its stages, with Orsini et al. identifying stages based on clinical presentation and Troscher, et al. focusing on pathogenesis.

on about December 9.[50] Dr. McCusker, in particular, viewed it as problematic that there would be any gap in time between the ongoing immune response underlying E.M.'s optic neuritis and the subsequent development of her Rasmussen's encephalitis. (Tr. 681-83.) In that regard, respondent contends that E.M.'s optic neuritis had fully resolved both clinically and radiologically by the time she began experiencing seizures on December 9, 2015. (ECF No. 128, p. 11.) More specifically, respondent argues that E.M.'s optic neuritis appears to have resolved by October 1, 2015. (*Id.* at 3 (citing Ex. 6, pp. 5-11, 14-20; Ex. 7, p. 157).) However, this is not credible.

While E.M. had a good clinical recovery and her vision did return to normal early-on, petitioners are persuasive in contending that E.M.'s good clinical recovery is not evidence of a complete recovery. The October 1, 2015 encounter with Dr. Digre cited by respondent indicates that E.M.'s vision had stabilized, but also confirms by physical exam that E.M. was still experiencing left-sided optic disk swelling. (Ex. 6, pp. 14-20.) E.M. was diagnosed with optic neuritis at that encounter and was only subsequently treated with steroids for the condition. (*Id*. at 16-17.) No repeat MRI was conducted until after the relevant period, after onset of what was later diagnosed as Rasmussen's encephalitis. Respondent and Dr. Linnoila additionally stress the November 10, 2015 notation by Dr. Lloyd that E.M. was "back to normal." (ECF No. 128, p. 10; Ex. 115, p. 244; Tr. 350.) However, this notation is in specific reference to E.M.'s vision. As previously noted, Dr. Digre had likewise recorded as of October 1, 2015, that E.M. was "fine" and with "good vision" while still also finding the continued presence of a swollen optic nerve upon physical exam. (Ex. 6, pp. 14, 16-17.) Although the November 10, 2015 encounter observed the fundi were clear "overall," resolution of the optic disk swelling was not specifically confirmed, the impression remained left-sided optic neuritis, and continued monitoring was planned. (Ex. 115, pp. 244-45.) Accordingly, the November 10, 2015 encounter is not dispositive of whether there was a complete resolution of E.M.'s optic neuritis. E.M. was not seen again until after she experienced the clinical onset of her Rasmussen's encephalitis.

Additionally, while optic neuritis was not specifically observed in E.M.'s subsequent December 12, 2015 MRI, that MRI study noted that the eye orbits were "not specifically studied."[51] (Ex. 134, pp. 498-99.) Thus, Dr. Steinman persuasively

[50] Respondent argues in his post-hearing brief that "E.M.'s optic neuritis could not have caused her December 9, 2015 seizures, and accordingly, could not have caused her Rasmussen's encephalitis." (ECF No. 128, p. 11 (emphasis omitted).) However, contrary to this framing, the question at issue is not whether E.M.'s optic neuritis directly caused her seizures. The seizures were a result of the Rasmussen's encephalitis under either party's understanding of the issue. (ECF No. 127, p. 21; ECF No. 128, p. 6; ECF No. 129, p. 32.) Rather, the question is whether, consistent with Dr. McCusker's explanation of the disease process, the inflammation due to optic neuritis was present at stage zero of the development of Rasmussen's encephalitis, such that it could have been attractant to the commencing Rasmussen's-related T cell responders in stage one that ultimately propagated the proposed autoantibody response that then culminated in the acute phase of Rasmussen's encephalitis at stage two, which began clinically on or about December 9, 2015.

[51] During the hearing, Dr. Linnoila did present images from the December 12 scan that she indicated show a lack of enhancement of the left optic nerve; however, she acknowledged that the optic nerve is "pretty hard to see" in the image. (Tr. 413-14.)

explained that the later December 29, 2015 MRI, which did examine the eye orbits, did confirm enhancement of the left optic nerve, consistent with ongoing optic neuritis. (Tr. 767-68; *see also* Ex. 8, pp. 1290-91.) Therefore, regardless of clinical history, there is objective evidence demonstrating that E.M.'s optic neuritis had not resolved at any point prior to the clinical onset of her Rasmussen's encephalitis. With regard to the additional left temporal lobe lesion identified from the September 2015 scan, the fact that it was not visible on the December 12, 2015 scan is not necessarily dispositive, given the limitations of the December 12, 2015 scan as explained by Dr. Silverman. (Tr. 282-83, 314-15, 572-91.) But, in any event, as explained above, petitioners need not specifically prove that this lesion persisted up until seizure onset in order to be casually relevant. Even assuming *arguendo* that Dr. Linnoila is more persuasive than Dr. Silverman in concluding the less sensitive MRI would still have detected the left temporal lobe lesion if it remained present during the December 12 scan, it would still be speculative giving the timing of the two MRI studies to attempt to pinpoint the date of its resolution as occurring prior to the mid-October to Mid-November period discussed above. Although Dr. Linnoila sought during the hearing to bolster her radiographic interpretation with clinical correlation (Tr. 413-15), she had initially opined that E.M.'s December 10, 2015 lumbar puncture results, which showed improved but ongoing pleocytosis, was consistent with a still resolving optic neuritis (Ex. C, p. 8).

Based on all of the above, there is preponderant evidence that E.M.'s optic neuritis occurred (and was ongoing) during a timeframe from which it is medically and scientifically reasonable to draw a causal inference implicating her optic neuritis as a cause of her later manifesting Rasmussen's encephalitis.

iii. <u>There is preponderant evidence of a logical sequence of cause and effect causally connecting E.M.'s optic neuritis and Rasmussen's encephalitis (*Althen* prong two)</u>

Even having established that optic neuritis can contribute to the development of Rasmussen's encephalitis, and even having established that the temporal association is present, petitioners must also demonstrate a logical sequence of cause and effect that implicates the optic neuritis as a factor in the development of E.M.'s own condition. *Althen*, 418 F.3d at 1278; *Wright*, 22 F.4th at 1004-06 (citing *Shyface*, 165 F.3d at 1352). Based on the parties' presentations, three considerations warrant discussion. First, was E.M.'s own condition consistent with the above-discussed theory? Second, how did E.M.'s treating physicians approach the relationship, if any, between the two conditions at issue? And, third, is respondent in any event persuasive in contending that a proposed HSV infection is sufficient explanation in itself for the development of E.M.'s Rasmussen's encephalitis?

E.M. was first seen for what was later diagnosed as optic neuritis on September 15, 2015, with a one-month history of vision disturbance in her left eye.[52] (Ex. 5, p. 3;

[52] When E.M. later presented to neuro-ophthalmologist Dr. Digre, it was indicated that E.M. did initially have symptoms in both eyes, but as the symptoms worsened, the condition progressed to affecting only the left eye. (Ex. 6, p. 5.) Upon examination, only left-side optic nerve swelling was ever observed. (*Id.*

see also Ex. 6, pp. 1-4.) She was referred to neuro-ophthalmology where she was assessed with a swollen left optic nerve and optic neuropathy, suspected of being papilledema due to optic neuritis. (Ex. 6, p. 9.) Follow-up MRIs were completed on September 25, 2015, showing abnormal enlargement and enhancement of the left (but not right) optic nerve, as well as multiple small nonspecific foci of subcortical white matter. (Ex. 8, pp. 740, 743.) E.M. was subsequently diagnosed with left optic neuritis and, though the radiology report indicated the relationship between the white matter foci and optic neuritis is unclear and with no indication of active demyelination (*Id.* at 742-43), a broader demyelinating disorder such as ADEM was also suspected as a matter of clinical correlation (Ex. 6, p. 17).

Both Drs. Steinman and Linnoila agree with the optic neuritis diagnosis. (Ex. 23, p. 40; Ex. C, p. 6.) However, while Dr. Steinman was more willing to at least entertain the ADEM diagnosis suggested by the treating physicians (Ex. 23, p. 40; Tr. 175.), Drs. Silverman and Linnoila both observed that E.M.'s scattered brain lesions were not disseminated and were non-specific (Tr. 311-13, 435-36, 446-49, 592), counseling against an ADEM diagnosis. Nonetheless, Dr. Silverman presented imaging during the hearing showing that E.M.'s September 25, 2015 MRI evidenced a left temporal lobe lesion that was not specifically identified in the radiology report. (*Id.* at 304-05.) Ultimately, while Dr. Linnoila maintained that the scattered nonspecific foci observed in the radiology report were not necessarily related to E.M.'s optic neuritis, she did agree that the lesion identified by Dr. Silverman was likely a part of E.M.'s optic neuritis.[53] (*Compare id.* at 496-97 (noting the radiologist's notation that the relationship between the September 25, 2015 MRI findings and optic neuritis was "unclear"), *with id.* at 420-27 (agreeing that the lesion identified by Dr. Silverman "is part of the process of the optic neuritis").) Accordingly, there is preponderant evidence that E.M. suffered left-side optic neuritis, inclusive of left-side brain pathology, which is therefore ipsilateral to her subsequent primarily left-side Rasmussen's encephalitis.

Additionally, E.M.'s subsequently occurring encephalitis was confirmed as a T-cell mediated form of encephalitis by brain biopsy. (Ex. 19; Ex. 8, p. 1854; Tr. 126, 206.) This demonstrates that E.M.'s own encephalitis is consistent with the pathophysiologic explanation of Rasmussen's encephalitis discussed in section (VI)(b)(i), *supra*. Although the Mayo Clinic autoimmune panel does include some NMDA receptors, it does not include the specific glutamate receptors implicated by Dr. Steinman's theory. (Ex. C, p. 12.) Accordingly, Dr. Linnoila acknowledged that further confirmation in the

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at 8-9.) Dr. Thorell's subsequent VAERS report also indicated that the initial optic neuritis was bilateral (Ex. 139, p. 3); however, Dr. Thorell was not involved in the diagnosis and treatment of E.M.'s initial optic neuritis. E.M. was never diagnosed as having bilateral optic neuritis.

[53] Dr. Linnoila initially felt that the left temporal lobe lesion was an old, chronic abnormality, but eventually agreed that it was related to E.M.'s optic neuritis. (Tr. 421-26, 438-41, 501-02, 567-68.) Lesions typically only enhance for about two weeks. *Greenslade v. Sec'y of Health & Human Servs.,* No. 14-1140V, 2024 WL 3527665, at *28 (Fed. Cl. Spec. Mstr. June 28, 2024). While Dr. Linnoila noted that the lesion cannot be dated due to the lack of enhancement, E.M.'s first MRI was on September 25, 2015, over a month post-vaccination, meaning it cannot be identified as pre-dating the vaccination.

form of antibody testing for the type of glutamate receptors implicated by Dr. Steinman's theory would be beyond the scope of what is available in an ordinary clinical setting using commercial labs. (*Id.* at 13.) To the extent there has been some indication that E.M. had predominantly, rather than exclusively, left-sided brain lesions, Fauser et al. preclude only exclusively contralateral lesions from their hypothesis. (Fauser et al., *supra*, at Ex. H, Tab 4, pp. 10-11.) But in any event, the treating physicians doubted whether any of the MRI findings relative to E.M.'s right hemisphere, which were stable, were relevant to the progressive findings affecting her left hemisphere. (Ex. 8, p. 1909 (explaining that "[s]mall focus of T2 hyperintensity in the right periventricular white matter is unchanged over all 4 imaging examinations dating to 9/25/2015, and may be chronic and unrelated to the findings of concern in the left cerebral hemisphere"); Ex. 8, p. 1853 (noting "isolated involvement of left hemisphere" supports Rasmussen's encephalitis).) And, as discussed in section (VI)(b)(ii), *supra*, there is preponderant evidence that E.M.'s optic neuritis persisted up-to and after the onset of her seizure disorder, meaning that the timing of the clinical onset of the encephalitis is appropriate for a causal inference for the reasons discussed above. Apart from the preponderantly supported presence of optic neuritis, respondent has not identified any other brain pathology that could otherwise explain the uni-hemisphere presentation of E.M.'s Rasmussen's encephalitis.

Thus, there is clinical evidence in this case sufficient to support a logical sequence of cause-and-effect implicating E.M.'s optic neuritis as a cause of her later developing Rasmussen's encephalitis.

Nonetheless, respondent's experts suggest that E.M. suffered optic neuritis and then – lightning striking twice – suffered an entirely unrelated Rasmussen's encephalitis a short time later. However, this conclusion is in tension with the clinical judgment of the treating physicians who were charged in the first instance with making sense of this highly unusual disease pattern. In fact, both parties' positions are in some tension with the treating physicians. The probative value of the treating physician opinions is reduced on the whole due to the lack of a clear diagnosis throughout much of E.M.'s early treatment. However, there is a clear pattern wherein the treating physicians repeatedly incorporated E.M.'s earlier optic neuritis into their evaluation of her clinical picture, which actually contributed to their hesitancy in diagnosing Rasmussen's encephalitis.

Yet, as previously addressed, Dr. Thorell, an infectious disease specialist, submitted a VAERS report as of January 13, 2016, in which she reported both E.M.'s optic neuritis and her subsequent epileptic presentation as an adverse event following her July 2015 HPV vaccination. (Ex. 139, p. 3.) Respondent focuses on that part of the submission that indicates that ADEM remained within the differential diagnosis (ECF No. 128, p. 24); however, Dr. Thorell described E.M.'s adverse event as optic neuritis with later developing syndrome inclusive of "difficult-to-manage seizures" and "multifocal encephalitis" (Ex. 139, p. 3). Dr. Thorell explained that, at that point, a "[b]road workup of autoimmune infectious, [and] oncologic etiologies" was unrevealing, but that "[a]n inflammatory process of autoimmune or vasculitic etiology remains a primary differential

consideration." (*Id*.) Accordingly, Dr. Thorell's opinion cannot be reduced to one of narrowly proposing post-vaccinal ADEM even as ADEM was proposed as a potential unifying diagnosis. Indeed, the reason ADEM remained a part of E.M.'s differential diagnosis for so long is precisely because the treating physicians felt that E.M.'s earlier optic neuritis needed to be accounted for resolving the correct diagnosis. (Ex. 8, p. 1816 (noting that E.M. "has a diagnosis of T-cell mediated encephalitis similar to Rasmussen[']s encephalitis but does not fit the complete picture of Rasmussen[']s (optic neuritis preceding current issues)"); *id.* at 2026 (offering ADEM as a possible unifying diagnosis for both optic neuritis and subsequent seizure disorder); *id.* at 2038 ("Given the previous eye findings in conjunction with rapid progression of brain parenchymal lesions, additional differential considerations could include . . . atypical demyelinating (ADEM) process . . . .").) Although a clear diagnosis did not emerge immediately, the treating physicians, best positioned to assess a logical sequence of cause and effect, were hesitant or unwilling to conclude based on the pattern of E.M.'s own clinical presentation that her earlier optic neuritis was entirely unrelated to her subsequent condition. Despite continued uncertainty, they did identify a diagnostic framing that accords with what petitioners have proposed. As of January 24, 2015, E.M.'s neurology team diagnosed "[p]robable autoimmune encephalopathy/encephalitis, features suggestive of [R]asmussen's encephalitis, with prior optic neuritis." (Ex. 8, p. 1825.) Though neither binding nor sacrosanct, treating physician opinions are probative and are often afforded considerable weight in themselves. *Andreu*, 569 F.3d at 1375-76; *Capizzano*, 440 F.3d at 1326.

Finally, respondent's experts both opine that E.M.'s Rasmussen's encephalitis was more likely caused by an HSV infection. (Tr. 502-07, 690-91.) Respondent's contention is primarily based on two observations. First, E.M. tested positive for HSV IgM and later IgG. (*Id.* at 506, 691, 739-40.) Second, E.M. experienced fevers prior to onset of her seizures on December 9, 2015, and the records contain at least some reports of an illness (sore throat) in the days prior to seizure onset. (*Id.* at 521-22, 689-90, 740.) Petitioners dispute both points.

According to Dr. Steinman, E.M.'s reported fevers are likely a consequence of the Rasmussen's encephalitis prodrome itself, especially given that seizures themselves can increase body temperature. (Tr. 802-03.) To that point, there are conflicting notations with respect to whether E.M. was suffering any other potential symptoms of infection. Although one record documents a reported sore throat, another contemporaneous record explicitly denies any preceding illness. (*Compare* Ex. 134, p. 540 (December 9, 2015 notation of 2-day history of sore throat), *with* Ex. 8, p. 578 (December 9, 2015 notion of "no recent illness").) Further to this, Dr. Steinman stresses that E.M. underwent extensive workup for an infectious cause of her condition and none was identified. (Tr. 112.) And, notably, while an infectious cause was included in E.M.'s differential diagnosis, none of E.M.'s medical records actually conclude that her condition was caused by an infection. (*See, e.g.*, Ex. 8, p. 2033 (January 13, 2016 rheumatology note that "infectious process seems unlikely"); *id.* at 1761-62 (January 28, 2016 discharge summary noting that "patient was afebrile and no infections were identified").) At best, the treating physicians felt based on the HSV serology that an

HSV infection could not be definitively excluded as a possible trigger for E.M.'s condition. (*Id.* at 1854.)

But in any event, respondent's experts are unpersuasive to the extent they opine that an HSV infection, if it occurred, would constitute the *sole* cause of E.M.'s Rasmussen's encephalitis. As explained above, Dr. McCusker opined that the development of Rasmussen's encephalitis requires some kind of antigen-presenting lesion within the brain that would attract T-cells in a uni-hemisphere pattern. (Tr. 673-78.) Thus, especially because infection has otherwise been associated with Rasmussen's encephalitis, Dr. McCusker opined that HSV within E.M.'s brain would have acted as that attractant. (*Id.* at 691-93.) However, while this is consistent with one theory of causation for Rasmussen's encephalitis, Dr. Steinman stressed that E.M. was specifically tested for HSV in her cerebral spinal fluid and biopsy tissue and it was not present.[54] (*Id.* at 112-18.) Thus, he opined that E.M.'s condition was autoinflammatory, but with no HSV (or any) infection within the central nervous system. (*Id.* at 118-21, 776-77, 800.) This is consistent with how the treating infectious disease specialist viewed the issue. (Ex. 8, p. 1854 (noting that "it is not possible to exclude the possibility that HSV could have triggered an immune response *in part* responsible for this disease (even if there is no evidence of HSV in the brain" (emphasis added)).) Therefore, Dr. McCusker's causal opinion relative to HSV infection in the central nervous system is unpersuasive as applied to the facts of this case based on objective evidence in E.M.'s own clinical history.

Consistent with the treating physicians, Dr. Linnoila nonetheless opines that it is not unusual for an infection in the periphery to commence an autoimmune process in the central nervous system, carefully distinguishing E.M.'s condition from a herpes encephalitis that would involve a direct viral infection within the central nervous system. (Tr. 356-60, 505-07; *see also* Ex. 8, p. 1835 (noting viruses can cause autoimmune encephalitis); *id.* at 1854 (noting HSV need not be evident in the brain to trigger an immune response leading to E.M.'s condition).) Notably, however, Dr. Linnoila's explanation, though it accounts for the lack of HSV in E.M.'s cerebral spinal fluid and biopsy, lacks any identification of a predisposing factor, such as the direct central nervous system infection otherwise posited by Dr. McCusker, and therefore fails to distinguish E.M.'s presentation from Dr. Steinman's two-hit explanation for the development of Rasmussen's encephalitis. In effect, she merely posits that an HSV infection outside the central nervous system, rather than the flu vaccine, would be the source of inflammation that acted as the second hit. (Tr. 357-59.) Yet, Dr. McCusker was clear in opining on respondent's behalf that, immunologically, some kind of predisposing abnormality within the left-hemisphere was necessary to explain how an autoimmune attack could occur in a uni-hemisphere pattern. (*Id.* at 675.) Neither Dr. Linnoila nor Dr. McCusker has explained how, absent such a predisposing abnormality, Rasmussen's encephalitis would take hold predominantly in E.M.'s left hemisphere following a peripheral HSV infection. Therefore, because E.M.'s left-side optic neuritis

[54] Some of E.M.'s medical records incorrectly indicate that her brain biopsy was positive for herpes. (*E.g.*, Ex. 8, pp. 1842-43.) However, the biopsy report confirms that immunostaining of the biopsy sample did not reveal the presence of either HSV 1 or 2. (Ex. 18, p. 2; Tr. 520.)

with brain lesion is preponderantly established, but an HSV infection within the central nervous system is not, Dr. Linnoila's opinion implicating a peripheral HSV infection does not readily call into question the additional causal role the optic neuritis in the development of E.M.'s Rasmussen's encephalitis.

Although the preceding optic neuritis alone would not explain E.M.'s development of Rasmussen's encephalitis, petitioners need not prove her vaccination to be the sole cause of her injury. *Shyface,* 165 F.3d at 1352-53; *see also Wright*, 22 F.4th at 1005 (explaining that a vaccine injury need only be a but for cause and substantial contributing factor of any complication or residual effect, rather than a predominant factor). Petitioners have established a logical sequence of cause and effect whereby E.M.'s vaccine-caused optic neuritis substantially contributed to, and was a but for cause of, her Rasmussen's encephalitis. This remains true regardless of whether the final trigger leading to Rasmussen's encephalitis was E.M.'s flu vaccination as petitioners contend, a peripheral HSV infection as respondent contends, or a combined effect of both.[55]

VII. Conclusion

After weighing the evidence of record within the context of the program, I find by preponderant evidence that E.M.'s optic neuritis was caused-in-fact by her HPV vaccination. I further find by preponderant evidence that E.M.'s HPV vaccination was a but for cause and substantial contributing factor in the development of her subsequent Rasmussen's encephalitis, given that the vaccine-caused optic neuritis was a cause of the Rasmussen's encephalitis. Petitioners are therefore entitled to compensation for these injuries. A separate damages order will issue.

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master

[55] This analysis also suffices to explain why respondent likewise has not met his own shifted burden of proof to demonstrate that E.M.'s injury was due to any factor unrelated to her vaccination. § 300aa-13(a)(1)(B); *Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013). In order to meet his burden, respondent must demonstrate by preponderant evidence "that a particular agent or condition (or multiple agents/conditions) unrelated to the vaccine was in fact the sole cause (thus excluding the vaccine as a substantial factor)." *de Bazan*, 539 F.3d at 1354 (emphasis omitted). As with petitioner's burden under *Althen*, respondent must show a logical sequence of cause and effect linking the injury to the proposed factor unrelated. *Deribeaux*, 717 F.3d at 1368-69. It need not be scientifically certain but must be legally probable. *Id*. Significantly, the Federal Circuit has rejected the contention that the presence of a viral infection can *per se* be considered a factor unrelated to vaccination. *Knudsen*, 35 F.3d at 548-50. Rather, respondent bears a burden of proving not only that there was a viral infection, but also that the infection was principally responsible for causing petitioner's injury. *Id.* (citing §300aa-13(a)(2)). Here, for the reasons discussed above, respondent has not substantiated that the infection, if it occurred, would have been the sole cause of the Rasmussen's encephalitis to the exclusion of the vaccine-caused optic neuritis. Although respondent also disputes that E.M.'s optic neuritis was vaccine caused, he has not proposed any factor unrelated to vaccination as a cause of that condition. (ECF No. 128, pp. 28-30.)